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(54) Title: PHENYLALANINE DERIVATIVES AS DIPEPTIDYL PEPTIDASE INHIBITORS FOR THE TREATMENT OR PREVENTION OF DIABETES

(57) Abstract: The present invention is directed to phenylalanine derivatives which are inhibitors of the dipeptidyl peptidase-IV enzyme ("DP-IV inhibitors") and which are useful in the treatment or prevention of diseases in which the dipeptidyl peptidase-IV enzyme is involved, such as diabetes and particularly type 2 diabetes. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which the dipeptidyl peptidase-IV enzyme is involved.

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## TITLE OF THE INVENTION

## PHENYLALANINE DERIVATIVES AS DIPEPTIDYL PEPTIDASE INHIBITORS FOR THE TREATMENT OR PREVENTION OF DIABETES

## 5 BACKGROUND OF THE INVENTION

Diabetes refers to a disease process derived from multiple causative factors and characterized by elevated levels of plasma glucose or hyperglycemia in the fasting state or after administration of glucose during an oral glucose tolerance test. Persistent or uncontrolled hyperglycemia is associated with increased and premature morbidity and mortality. Often  
10 abnormal glucose homeostasis is associated both directly and indirectly with alterations of the lipid, lipoprotein and apolipoprotein metabolism and other metabolic and hemodynamic disease. Therefore patients with Type 2 diabetes mellitus are at especially increased risk of macrovascular and microvascular complications, including coronary heart disease, stroke, peripheral vascular disease, hypertension, nephropathy, neuropathy, and retinopathy. Therefore, therapeutical  
15 control of glucose homeostasis, lipid metabolism and hypertension are critically important in the clinical management and treatment of diabetes mellitus.

There are two generally recognized forms of diabetes. In type 1 diabetes, or insulin-dependent diabetes mellitus (IDDM), patients produce little or no insulin, the hormone which regulates glucose utilization. In type 2 diabetes, or noninsulin dependent diabetes mellitus  
20 (NIDDM), patients often have plasma insulin levels that are the same or even elevated compared to nondiabetic subjects; however, these patients have developed a resistance to the insulin stimulating effect on glucose and lipid metabolism in the main insulin-sensitive tissues, which are muscle, liver and adipose tissues, and the plasma insulin levels, while elevated, are insufficient to overcome the pronounced insulin resistance.

25 Insulin resistance is not primarily due to a diminished number of insulin receptors but to a post-insulin receptor binding defect that is not yet understood. This resistance to insulin responsiveness results in insufficient insulin activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in the liver.

30 The available treatments for type 2 diabetes, which have not changed substantially in many years, have recognized limitations. While physical exercise and reductions in dietary intake of calories will dramatically improve the diabetic condition, compliance with this treatment is very poor because of well-entrenched sedentary lifestyles and excess food consumption, especially of foods containing high amounts of saturated fat. Increasing the plasma

level of insulin by administration of sulfonylureas (e.g. tolbutamide and glipizide) or meglitinide, which stimulate the pancreatic  $\beta$ -cells to secrete more insulin, and/or by injection of insulin when sulfonylureas or meglitinide become ineffective, can result in insulin concentrations high enough to stimulate the very insulin-resistant tissues. However, dangerously low levels of plasma glucose can result from administration of insulin or insulin secretagogues (sulfonylureas or meglitinide), and an increased level of insulin resistance due to the even higher plasma insulin levels can occur. The biguanides increase insulin sensitivity resulting in some correction of hyperglycemia. However, the two biguanides, phenformin and metformin, can induce lactic acidosis and nausea/diarrhea. Metformin has fewer side effects than phenformin and is often prescribed for the treatment of Type 2 diabetes.

The glitazones (i.e. 5-benzylthiazolidine-2,4-diones) are a more recently described class of compounds with potential for ameliorating many symptoms of type 2 diabetes. These agents substantially increase insulin sensitivity in muscle, liver and adipose tissue in several animal models of type 2 diabetes resulting in partial or complete correction of the elevated plasma levels of glucose without occurrence of hypoglycemia. The glitazones that are currently marketed are agonists of the peroxisome proliferator activated receptor (PPAR), primarily the PPAR-gamma subtype. PPAR-gamma agonism is generally believed to be responsible for the improved insulin sensitization that is observed with the glitazones. Newer PPAR agonists that are being tested for treatment of Type II diabetes are agonists of the alpha, gamma or delta subtype, or a combination of these, and in many cases are chemically different from the glitazones (i.e., they are not thiazolidinediones). Serious side effects (e.g. liver toxicity) have occurred with some of the glitazones, such as troglitazone.

Additional methods of treating the disease are still under investigation. New biochemical approaches that have been recently introduced or are still under development include treatment with alpha-glucosidase inhibitors (e.g. acarbose) and protein tyrosine phosphatase-1B (PTP-1B) inhibitors.

Compounds that are inhibitors of the dipeptidyl peptidase-IV ("DP-IV" or "DPP-IV") enzyme are also under investigation as drugs that may be useful in the treatment of diabetes, and particularly type 2 diabetes. See for example WO 97/40832, WO 98/19998, U.S. Patent No. 5,939,560, Bioorg. Med. Chem. Lett., 6: 1163-1166 (1996); and Bioorg. Med. Chem. Lett., 6: 2745-2748 (1996). The usefulness of DP-IV inhibitors in the treatment of type 2 diabetes is based on the fact that DP-IV *in vivo* readily inactivates glucagon like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP). GLP-1 and GIP are incretins and are produced when food is consumed. The incretins stimulate production of insulin. Inhibition of DP-IV leads to decreased

inactivation of the incretins, and this in turn results in increased effectiveness of the incretins in stimulating production of insulin by the pancreas. DP-IV inhibition therefore results in an increased level of serum insulin. Advantageously, since the incretins are produced by the body only when food is consumed, DP-IV inhibition is not expected to increase the level of insulin at inappropriate times, such as between meals, which can lead to excessively low blood sugar (hypoglycemia). Inhibition of DP-IV is therefore expected to increase insulin without increasing the risk of hypoglycemia, which is a dangerous side effect associated with the use of insulin secretagogues.

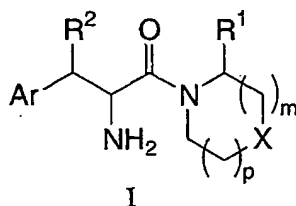
DP-IV inhibitors also have other therapeutic utilities, as discussed herein. DP-IV inhibitors have not been studied extensively to date, especially for utilities other than diabetes. New compounds are needed so that improved DP-IV inhibitors can be found for the treatment of diabetes and potentially other diseases and conditions.

#### SUMMARY OF THE INVENTION

The present invention is directed to phenylalanine derivatives which are inhibitors of the dipeptidyl peptidase-IV enzyme ("DP-IV inhibitors") and which are useful in the treatment or prevention of diseases in which the dipeptidyl peptidase-IV enzyme is involved, such as diabetes and particularly type 2 diabetes. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which the dipeptidyl peptidase-IV enzyme is involved.

#### DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to phenylalanine derivatives useful as inhibitors of dipeptidyl peptidase-IV. Compounds of the present invention are described by structural formula I:



or a pharmaceutically acceptable salt thereof; wherein each n is independently 0, 1, or 2;

m and p are independently 0 or 1;

q is 1 or 2;

X is CH<sub>2</sub>, S, CHF or CF<sub>2</sub>;

5

Ar is phenyl, unsubstituted or substituted with one to five R<sup>3</sup> substituents;

R<sup>1</sup> is hydrogen or cyano;

10 R<sup>2</sup> is selected from the group consisting of

C<sub>1-10</sub> alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents independently selected from halogen or hydroxy,

C<sub>2-10</sub> alkenyl, wherein alkenyl is unsubstituted or substituted with one to five substituents independently selected from halogen or hydroxy,

15 (CH<sub>2</sub>)<sub>n</sub>-aryl, wherein aryl is unsubstituted or substituted with one to five substituents independently selected hydroxy, halogen, CO<sub>2</sub>H, C<sub>1-6</sub> alkyloxycarbonyl, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,

20 (CH<sub>2</sub>)<sub>n</sub>-heteroaryl, wherein heteroaryl is unsubstituted or substituted with one to three substituents independently selected from hydroxy, halogen, CO<sub>2</sub>H, C<sub>1-6</sub> alkyloxycarbonyl, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,

25 (CH<sub>2</sub>)<sub>n</sub>-heterocyclyl, wherein heterocyclyl is unsubstituted or substituted with one to three substituents independently selected from oxo, hydroxy, halogen, CO<sub>2</sub>H, C<sub>1-6</sub> alkyloxycarbonyl, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,

30 (CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub> cycloalkyl, wherein cycloalkyl is unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, CO<sub>2</sub>H, C<sub>1-6</sub> alkyloxycarbonyl, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,

(CH<sub>2</sub>)<sub>n</sub>COOH,

(CH<sub>2</sub>)<sub>n</sub>COOC<sub>1-6</sub> alkyl,

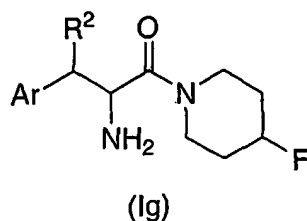
(CH<sub>2</sub>)<sub>n</sub>CONR<sup>4</sup>R<sup>5</sup>, wherein R<sup>4</sup> and R<sup>5</sup> are independently selected from the group consisting of hydrogen, tetrazolyl, thiazolyl, (CH<sub>2</sub>)<sub>n</sub>-phenyl, (CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub>

5 cycloalkyl, and C<sub>1-6</sub> alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens and wherein phenyl and cycloalkyl are unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens;  
or R<sup>4</sup> and R<sup>5</sup> together with the nitrogen atom to which they are attached form a heterocyclic ring selected from azetidine, pyrrolidine, piperidine, piperazine, and morpholine wherein said heterocyclic ring is unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens; and  
10 wherein any methylene (CH<sub>2</sub>) carbon atom in R<sup>2</sup> is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, C<sub>1-4</sub> alkyl, and C<sub>1-4</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens;  
15

each R<sup>3</sup> is independently selected from the group consisting of  
halogen,  
cyano,  
20 hydroxy,  
phenyloxy, unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, CO<sub>2</sub>H, cyano,  
C<sub>1-6</sub> alkyloxycarbonyl, C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens;  
25 C<sub>1-6</sub> alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens, C<sub>1-6</sub> alkoxy, wherein alkoxy is unsubstituted or substituted with one to five halogens,  
(CH<sub>2</sub>)<sub>n</sub>-NR<sup>4</sup>R<sup>5</sup>,  
(CH<sub>2</sub>)<sub>n</sub>-CONR<sup>4</sup>R<sup>5</sup>,  
(CH<sub>2</sub>)<sub>n</sub>-OCONR<sup>4</sup>R<sup>5</sup>,  
30 (CH<sub>2</sub>)<sub>n</sub>-SO<sub>2</sub>NR<sup>4</sup>R<sup>5</sup>,  
(CH<sub>2</sub>)<sub>n</sub>-SO<sub>2</sub>R<sup>6</sup>,  
(CH<sub>2</sub>)<sub>n</sub>-NR<sup>7</sup>SO<sub>2</sub>R<sup>6</sup>,  
(CH<sub>2</sub>)<sub>n</sub>-NR<sup>7</sup>CONR<sup>4</sup>R<sup>5</sup>,  
(CH<sub>2</sub>)<sub>n</sub>-NR<sup>7</sup>COR<sup>7</sup>,

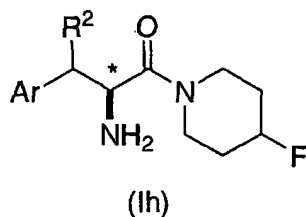
- (CH<sub>2</sub>)<sub>n</sub>-NR<sup>7</sup>CO<sub>2</sub>R<sup>6</sup>,  
(CH<sub>2</sub>)<sub>n</sub>-COOH,  
(CH<sub>2</sub>)<sub>n</sub>-COOC<sub>1-6</sub> alkyl,  
(CH<sub>2</sub>)<sub>q</sub>-aryl, wherein aryl is unsubstituted or substituted with one to five substituents  
5 independently selected from halogen, hydroxy, CO<sub>2</sub>H,  
C<sub>1-6</sub> alkyloxycarbonyl, C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, and C<sub>1-6</sub> alkoxy, wherein  
alkyl and alkoxy are unsubstituted or substituted with one to five halogens,  
(CH<sub>2</sub>)<sub>q</sub>-heteroaryl, wherein heteroaryl is unsubstituted or substituted with one to three  
10 substituents independently selected from hydroxy, halogen, CO<sub>2</sub>H, C<sub>1-6</sub>  
alkyloxycarbonyl, C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl  
and alkoxy are unsubstituted or substituted with one to five halogens,  
(CH<sub>2</sub>)<sub>q</sub>-heterocyclyl, wherein heterocyclyl is unsubstituted or substituted with one to  
three substituents independently selected from oxo, hydroxy, halogen, CO<sub>2</sub>H, C<sub>1-6</sub>  
15 alkyloxycarbonyl, C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl  
and alkoxy are unsubstituted or substituted with one to five halogens,  
(CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub> cycloalkyl, wherein cycloalkyl is unsubstituted or substituted with one to  
three substituents independently selected from halogen, hydroxy, C<sub>1-6</sub> alkyl, and  
C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one  
20 to five halogens,  
wherein any methylene (CH<sub>2</sub>) carbon atom in R<sup>3</sup> is unsubstituted or substituted with one  
to two groups independently selected from halogen, hydroxy, C<sub>1-4</sub> alkyl, and C<sub>1-4</sub>  
alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five  
halogens;  
25 R<sup>6</sup> is independently selected from the group consisting of tetrazolyl, thiazolyl, (CH<sub>2</sub>)<sub>n</sub>-phenyl,  
(CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub> cycloalkyl, and C<sub>1-6</sub> alkyl, wherein alkyl is unsubstituted or substituted with one  
to five halogens and wherein phenyl and cycloalkyl are unsubstituted or substituted with one to  
five substituents independently selected from halogen, hydroxy, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy,  
wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens, and wherein  
30 any methylene (CH<sub>2</sub>) carbon atom in R<sup>6</sup> is unsubstituted or substituted with one to two groups  
independently selected from halogen, hydroxy, C<sub>1-4</sub> alkyl, and C<sub>1-4</sub> alkoxy, wherein alkyl and  
alkoxy are unsubstituted or substituted with one to five halogens; and

each R<sup>7</sup> is hydrogen or R<sup>6</sup>.



wherein Ar and R<sup>2</sup> are as defined herein.

In a class of this embodiment of the compounds of the present invention, the  
 5 carbon atom marked with an \* has the stereochemical configuration as depicted in formula Ih:



wherein Ar and R<sup>2</sup> are as defined herein.

- In a fifth embodiment of the compounds of the present invention,
- 10 R<sup>2</sup> is selected from the group consisting of
- C<sub>1-6</sub> alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents independently selected from halogen or hydroxy,
  - C<sub>2-6</sub> alkenyl, wherein alkenyl is unsubstituted or substituted with one to five substituents independently selected from halogen or hydroxy,
  - 15 (CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub> cycloalkyl, wherein cycloalkyl is unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, CO<sub>2</sub>H, C<sub>1-6</sub> alkyloxycarbonyl, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,
  - (CH<sub>2</sub>)<sub>n</sub>COOH,
  - 20 (CH<sub>2</sub>)<sub>n</sub>COOC<sub>1-6</sub> alkyl, and
  - (CH<sub>2</sub>)<sub>n</sub>CONR<sup>4</sup>R<sup>5</sup>, wherein R<sup>4</sup> and R<sup>5</sup> are independently selected from the group consisting of hydrogen, tetrazolyl, thiazolyl, (CH<sub>2</sub>)<sub>n</sub>-phenyl, (CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub> cycloalkyl, and C<sub>1-6</sub> alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens and wherein phenyl and cycloalkyl are unsubstituted or



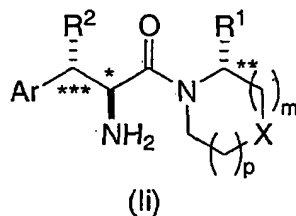
substituted with one to five substituents independently selected from halogen, hydroxy, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens;  
or R<sup>4</sup> and R<sup>5</sup> together with the nitrogen atom to which they are attached form a  
5 heterocyclic ring selected from pyrrolidine, piperidine, piperazine, and morpholine wherein said heterocyclic ring is unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens; and  
10 wherein any methylene (CH<sub>2</sub>) carbon atom in R<sup>2</sup> is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, C<sub>1-4</sub> alkyl, and C<sub>1-4</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens.

15 In a class of this embodiment of the compounds of the present invention, R<sup>2</sup> is selected from the group consisting of  
C<sub>1-3</sub> alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents independently selected from halogen or hydroxy,  
CH<sub>2</sub>-C<sub>3-6</sub> cycloalkyl,  
20 COOH,  
COOC<sub>1-6</sub> alkyl, and  
CONR<sup>4</sup>R<sup>5</sup>, wherein R<sup>4</sup> and R<sup>5</sup> are independently selected from the group consisting of hydrogen, tetrazolyl, thiazolyl, (CH<sub>2</sub>)<sub>n</sub>-phenyl, (CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub> cycloalkyl, and C<sub>1-6</sub> alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens and  
25 wherein phenyl and cycloalkyl are unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens;  
or R<sup>4</sup> and R<sup>5</sup> together with the nitrogen atom to which they are attached form a  
30 heterocyclic ring selected from pyrrolidine, piperidine, piperazine, and morpholine wherein said heterocyclic ring is unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens.

In a subclass of this class,  $R^2$  is selected from the group consisting of:

5 methyl,  
ethyl,  
CH<sub>2</sub>-cyclopropyl,  
COOH,  
COOMe,  
COOEt,  
CONMe<sub>2</sub>,  
10 CONH<sub>2</sub>,  
CONHMe,  
CONHEt,  
pyrrolidin-1-ylcarbonyl,  
azetidin-1-ylcarbonyl, and  
15 [(tetrazol-5-yl)amino]carbonyl.

In a sixth embodiment of the compounds of the present invention, the carbon atom marked with an \* has the stereochemical configuration, the carbon atom attached to  $R^1$  and marked with an \*\* has the stereochemical configuration, and the carbon atom attached to  $R^2$  and  
20 marked with an \*\*\* has the stereochemical configuration as depicted in formula Ii:



wherein Ar, X, m, p and  $R^1$  are as defined herein;

$R^2$  is selected from the group consisting of  
25 C<sub>1-6</sub> alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents  
independently selected from halogen or hydroxy,  
(CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub> cycloalkyl,  
COOH,  
COOC<sub>1-6</sub>alkyl, and

- CONR<sup>4</sup>R<sup>5</sup>, wherein R<sup>4</sup> and R<sup>5</sup> are independently selected from the group consisting of hydrogen, tetrazolyl, thiazolyl, (CH<sub>2</sub>)<sub>n</sub>-phenyl, (CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub> cycloalkyl, and C<sub>1-6</sub> alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens and wherein phenyl and cycloalkyl are unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens;
- or wherein R<sup>4</sup> and R<sup>5</sup> together with the nitrogen atom to which they are attached form a heterocyclic ring selected from pyrrolidine, piperidine, piperazine, and morpholine wherein said heterocyclic ring is unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens; and
- each R<sup>3</sup> is independently selected from the group consisting of:
- halogen,
  - hydroxy,
  - C<sub>1-6</sub> alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens,
  - C<sub>1-6</sub> alkoxy, wherein alkoxy is unsubstituted or substituted with one to five halogens,
  - phenyloxy, unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, cyano, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens; and
  - (CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub> cycloalkyl, wherein cycloalkyl is unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens.

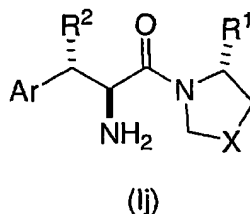
- In a class of this embodiment, R<sup>2</sup> is selected from the group consisting of:
- methyl,
  - ethyl,
  - CH<sub>2</sub>-cyclopropyl,
  - COOH,
  - COOMe,
  - COOEt,

CONMe<sub>2</sub>,  
 CONH<sub>2</sub>,  
 CONHMe,  
 CONHEt,  
 5 pyrrolidin-1-ylcarbonyl,  
 azetidin-1-ylcarbonyl, and  
 [(tetrazol-5-yl)amino]carbonyl.

In a subclass of this class, R<sup>3</sup> is selected from the group consisting of:

10 fluoro,  
 chloro,  
 bromo,  
 trifluoromethyl,  
 trifluoromethoxy, and  
 15 methoxy.

A seventh embodiment of the compounds of the present invention encompasses compounds of the formula Ij:



20 wherein X is CH<sub>2</sub>, S, CHF, or CF<sub>2</sub>;

Ar is phenyl, unsubstituted or substituted with one to five R<sup>3</sup> substituents;

R<sup>1</sup> is hydrogen or cyano;

25 R<sup>2</sup> is selected from the group consisting of

C<sub>1-6</sub> alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents  
 independently selected from halogen or hydroxy,  
 (CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub> cycloalkyl,  
 COOH,

COOC<sub>1-6</sub>alkyl, and

CONR<sup>4</sup>R<sup>5</sup>, wherein R<sup>4</sup> and R<sup>5</sup> are independently selected from the group consisting of hydrogen, tetrazolyl, thiazolyl, (CH<sub>2</sub>)<sub>n</sub>-phenyl, (CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub> cycloalkyl, and C<sub>1-6</sub> alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens and wherein phenyl and cycloalkyl are unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens;

or R<sup>4</sup> and R<sup>5</sup> together with the nitrogen atom to which they are attached form a heterocyclic ring selected from pyrrolidine, piperidine, piperazine, and morpholine wherein said heterocyclic ring is unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens; and

each R<sup>3</sup> is independently selected from the group consisting of:

halogen,

C<sub>1-6</sub> alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens,

C<sub>1-6</sub> alkoxy, wherein alkoxy is unsubstituted or substituted with one to five

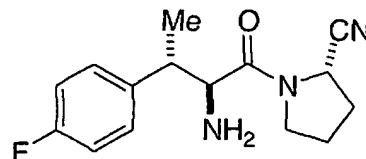
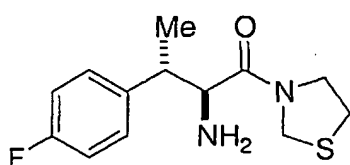
halogens,

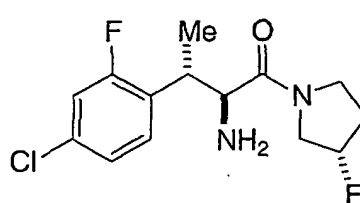
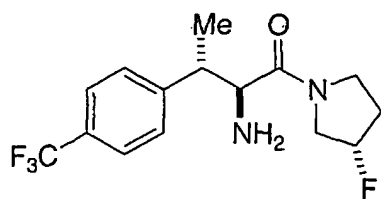
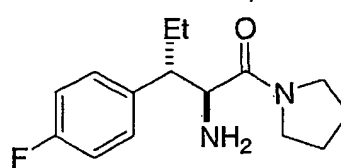
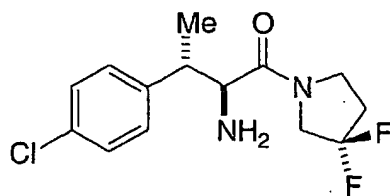
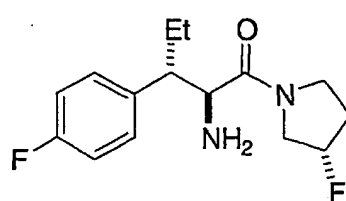
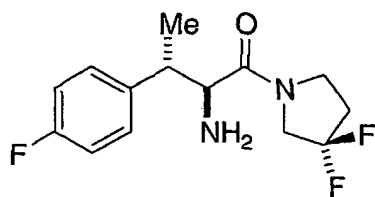
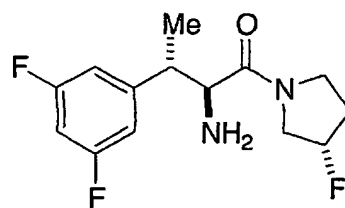
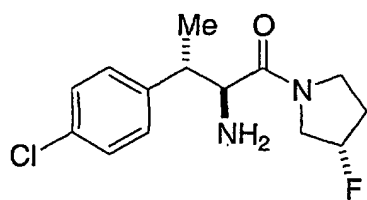
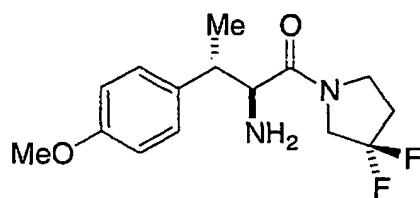
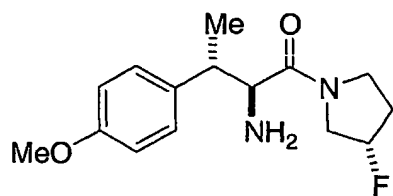
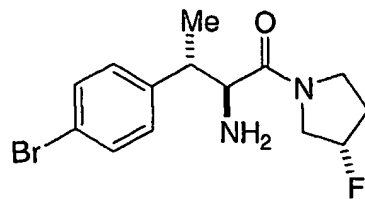
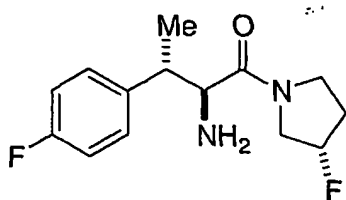
phenyloxy, unsubstituted or substituted with one to three substituents

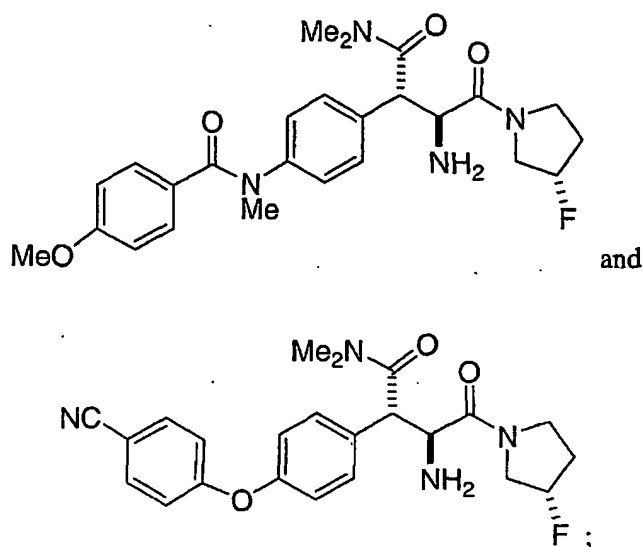
independently selected from halogen and cyano, and

phenyl(CH<sub>2</sub>)<sub>n</sub>CON(Me)-, wherein phenyl is unsubstituted or substituted with one to three substituents independently selected from halogen, trifluoromethyl, and C<sub>1-4</sub> alkyl.

Illustrative, but nonlimiting examples, of compounds of the present invention that are useful as dipeptidyl peptidase-IV inhibitors are the following:







or a pharmaceutically acceptable salt thereof.

5 As used herein the following definitions are applicable.

"Alkyl", as well as other groups having the prefix "alk", such as alkoxy and alkanoyl, means carbon chains which may be linear or branched, and combinations thereof, unless the carbon chain is defined otherwise. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl, and the like.

10 Where the specified number of carbon atoms permits, e.g., from C<sub>3</sub>-10, the term alkyl also includes cycloalkyl groups, and combinations of linear or branched alkyl chains combined with cycloalkyl structures. When no number of carbon atoms is specified, C<sub>1</sub>-6 is intended.

"Cycloalkyl" is a subset of alkyl and means a saturated carbocyclic ring having a specified number of carbon atoms. Examples of cycloalkyl include cyclopropyl, cyclobutyl, 15 cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like. A cycloalkyl group generally is monocyclic unless stated otherwise. Cycloalkyl groups are saturated unless otherwise defined.

The term "alkoxy" refers to straight or branched chain alkoxides of the number of carbon atoms specified (e.g., C<sub>1</sub>-6 alkoxy), or any number within this range [i.e., methoxy (MeO-), ethoxy, isopropoxy, etc.].

20 The term "alkylthio" refers to straight or branched chain alkylsulfides of the number of carbon atoms specified (e.g., C<sub>1</sub>-6 alkylthio), or any number within this range [i.e., methylthio (MeS-), ethylthio, isopropylthio, etc.].

The term "alkylamino" refers to straight or branched alkylamines of the number of carbon atoms specified (e.g., C<sub>1-6</sub> alkylamino), or any number within this range [i.e., methylamino, ethylamino, isopropylamino, t-butylamino, etc.].

5 The term "alkylsulfonyl" refers to straight or branched chain alkylsulfones of the number of carbon atoms specified (e.g., C<sub>1-6</sub> alkylsulfonyl), or any number within this range [i.e., methylsulfonyl (MeSO<sub>2</sub>-), ethylsulfonyl, isopropylsulfonyl, etc.].

10 The term "alkyloxycarbonyl" refers to straight or branched chain esters of a carboxylic acid derivative of the present invention of the number of carbon atoms specified (e.g., C<sub>1-6</sub> alkyloxycarbonyl), or any number within this range [i.e., methyloxycarbonyl (MeOCO-), ethyloxycarbonyl, or butyloxycarbonyl].

"Aryl" means a mono- or polycyclic aromatic ring system containing carbon ring atoms. The preferred aryls are monocyclic or bicyclic 6-10 membered aromatic ring systems. Phenyl and naphthyl are preferred aryls. The most preferred aryl is phenyl.

15 "Heterocycle" and "heterocyclyl" refer to saturated or unsaturated non-aromatic rings or ring systems containing at least one heteroatom selected from O, S and N, further including the oxidized forms of sulfur, namely SO and SO<sub>2</sub>. Examples of heterocycles include tetrahydrofuran (THF), dihydrofuran, 1,4-dioxane, morpholine, 1,4-dithiane, piperazine, piperidine, 1,3-dioxolane, imidazolidine, imidazoline, pyrroline, pyrrolidine, tetrahydropyran, dihydropyran, oxathiolane, dithiolane, 1,3-dioxane, 1,3-dithiane, oxathiane, thiomorpholine, and  
20 the like.

"Heteroaryl" means an aromatic or partially aromatic heterocycle that contains at least one ring heteroatom selected from O, S and N. Heteroaryls also include heteroaryls fused to other kinds of rings, such as aryls, cycloalkyls and heterocycles that are not aromatic. Examples of heteroaryl groups include pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridinyl, 2-  
25 oxo-(1*H*)-pyridinyl (2-hydroxy-pyridinyl), oxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, thiadiazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, triazinyl, thienyl, pyrimidinyl, pyrazinyl, benzisoxazolyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, dihydrobenzofuranyl, indolinyl, pyridazinyl, indazolyl, isoindolyl, dihydrobenzothienyl, indoliziny, cinnolinyl, phthalazinyl, quinazolinyl, naphthyridinyl, carbazolyl, benzodioxolyl,  
30 quinoxalinyl, purinyl, furazanyl, isobenzylfuranyl, benzimidazolyl, benzofuranyl, benzothienyl, quinolyl, indolyl, isoquinolyl, dibenzofuranyl, imidazo[1,2-*a*]pyridinyl, [1,2,4-triazolo][4,3-*a*]pyridinyl, pyrazolo[1,5-*a*]pyridinyl, [1,2,4-triazolo][1,5-*a*]pyridinyl, 2-oxo-1,3-benzoxazolyl, 4-oxo-3*H*-quinazolinyl, 3-oxo-[1,2,4]-triazolo[4,3-*a*]-2*H*-pyridinyl, 5-oxo-[1,2,4]-4*H*-oxadiazolyl, 2-oxo-[1,3,4]-3*H*-oxadiazolyl, 2-oxo-1,3-dihydro-2*H*-imidazolyl, 3-oxo-2,4-



dihydro-3*H*-1,2,4-triazolyl, and the like. For heterocyclyl and heteroaryl groups, rings and ring systems containing from 3-15 atoms are included, forming 1-3 rings.

"Halogen" refers to fluorine, chlorine, bromine and iodine. Chlorine and fluorine are generally preferred. Fluorine is most preferred when the halogens are substituted on an alkyl or alkoxy group (e.g. CF<sub>3</sub>O and CF<sub>3</sub>CH<sub>2</sub>O).

The compounds of the present invention may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. The compounds of the present invention have one asymmetric center at the carbon atom marked with an \* in formula Ia. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within the ambit of this invention. The present invention is meant to comprehend all such isomeric forms of these compounds.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

Some of the compounds described herein may exist as tautomers, which have different points of attachment of hydrogen accompanied by one or more double bond shifts. For example, a ketone and its enol form are keto-enol tautomers. The individual tautomers as well as mixtures thereof are encompassed with compounds of the present invention.

Formula I shows the structure of the class of compounds without preferred stereochemistry. Formula Ia shows the preferred stereochemistry at the carbon atom to which is attached the amino group of the alpha amino acid from which these compounds are prepared.

The independent syntheses of these diastereomers or their chromatographic separations may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.

If desired, racemic mixtures of the compounds may be separated so that the individual enantiomers are isolated. The separation can be carried out by methods well known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. The coupling reaction is often the formation of salts using an enantiomerically pure acid or base. The

diastomeric derivatives may then be converted to the pure enantiomers by cleavage of the added chiral residue. The racemic mixture of the compounds can also be separated directly by chromatographic methods utilizing chiral stationary phases, which methods are well known in the art.

5' Alternatively, any enantiomer of a compound may be obtained by stereoselective synthesis using optically pure starting materials or reagents of known configuration by methods well known in the art.

It will be understood that, as used herein, references to the compounds of structural formula I are meant to also include the pharmaceutically acceptable salts, and also salts that are not pharmaceutically acceptable when they are used as precursors to the free compounds or their pharmaceutically acceptable salts or in other synthetic manipulations.

The compounds of the present invention may be administered in the form of a pharmaceutically acceptable salt. The term "pharmaceutically acceptable salt" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts of basic compounds encompassed within the term "pharmaceutically acceptable salt" refer to non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid. Representative salts of basic compounds of the present invention include, but are not limited to, the following: acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide and valerate. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof include, but are not limited to, salts derived from inorganic bases including aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, mangamous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, cyclic amines, and basic ion-exchange resins, such as arginine, betaine, caffeine, choline, N,N-

dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

Also, in the case of a carboxylic acid (-COOH) or alcohol group being present in the compounds of the present invention, pharmaceutically acceptable esters of carboxylic acid derivatives, such as methyl, ethyl, or pivaloyloxymethyl, or acyl derivatives of alcohols, such as acetate or maleate, can be employed. Included are those esters and acyl groups known in the art for modifying the solubility or hydrolysis characteristics for use as sustained-release or prodrug formulations.

Solvates, and in particular, the hydrates of the compounds of structural formula I are included in the present invention as well.

Exemplifying the invention is the use of the compounds disclosed in the Examples and herein.

The subject compounds are useful in a method of inhibiting the dipeptidyl peptidase-IV enzyme in a patient such as a mammal in need of such inhibition comprising the administration of an effective amount of the compound. The present invention is directed to the use of the compounds disclosed herein as inhibitors of dipeptidyl peptidase-IV enzyme activity.

In addition to primates, such as humans, a variety of other mammals can be treated according to the method of the present invention. For instance, mammals including, but not limited to, cows, sheep, goats, horses, dogs, cats, guinea pigs, rats or other bovine, ovine, equine, canine, feline, rodent or murine species can be treated. However, the method can also be practiced in other species, such as avian species (e.g., chickens).

The present invention is further directed to a method for the manufacture of a medicament for inhibiting dipeptidyl peptidase-IV enzyme activity in humans and animals comprising combining a compound of the present invention with a pharmaceutically acceptable carrier or diluent.

The subject treated in the present methods is generally a mammal, preferably a human being, male or female, in whom inhibition of dipeptidyl peptidase-IV enzyme activity is desired. The term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. Such term in relation to pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The terms "administration of" and or "administering a" compound should be understood to mean providing a compound of the invention or a prodrug of a compound of the invention to the individual in need of treatment.

The utility of the compounds in accordance with the present invention as inhibitors of dipeptidyl peptidase-IV enzyme activity may be demonstrated by methodology known in the art. Inhibition constants are determined as follows. A continuous fluorometric assay is employed with the substrate Gly-Pro-AMC, which is cleaved by DP-IV to release the fluorescent AMC leaving group. The kinetic parameters that describe this reaction are as follows:  $K_m = 50 \mu\text{M}$ ;  $k_{cat} = 75 \text{ s}^{-1}$ ;  $k_{cat}/K_m = 1.5 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$ . A typical reaction contains approximately 50 pM enzyme, 50  $\mu\text{M}$  Gly-Pro-AMC, and buffer (100 mM HEPES, pH 7.5, 0.1 mg/ml BSA) in a total reaction volume of 100  $\mu\text{l}$ . Liberation of AMC is monitored continuously in a 96-well plate fluorometer using an excitation wavelength of 360 nm and an emission wavelength of 460 nm. Under these conditions, approximately 0.8  $\mu\text{M}$  AMC is produced in 30 min at 25 degrees C. The enzyme used in these studies was soluble (transmembrane domain and cytoplasmic extension excluded) human protein produced in a baculovirus expression system (Bac-To-Bac, Gibco BRL). The kinetic constants for hydrolysis of Gly-Pro-AMC and GLP-1 were found to be in accord with literature values for the native enzyme. To measure the dissociation constants for compounds, solutions of inhibitor in DMSO were added to reactions containing enzyme and substrate (final DMSO concentration is 1%). All experiments were conducted at room temperature using the standard reaction conditions described above. To determine the dissociation constants ( $K_i$ ), reaction rates were fit by non-linear regression to the

Michaelis-Menton equation for competitive inhibition. The errors in reproducing the dissociation constants are typically less than two-fold.

In particular, the compounds of the following examples had activity in inhibiting the dipeptidyl peptidase-IV enzyme in the aforementioned assays, generally with an IC<sub>50</sub> of less than about 1  $\mu$ M. Such a result is indicative of the intrinsic activity of the compounds in use as inhibitors the dipeptidyl peptidase-IV enzyme activity.

Dipeptidyl peptidase-IV enzyme (DP-IV) is a cell surface protein that has been implicated in a wide range of biological functions. It has a broad tissue distribution (intestine, kidney, liver, pancreas, placenta, thymus, spleen, epithelial cells, vascular endothelium, lymphoid and myeloid cells, serum), and distinct tissue and cell-type expression levels. DP-IV is identical to the T cell activation marker CD26, and it can cleave a number of immunoregulatory, endocrine, and neurological peptides *in vitro*. This has suggested a potential role for this peptidase in a variety of disease processes in humans or other species.

Accordingly, the subject compounds are useful in a method for the prevention or treatment of the following diseases, disorders and conditions.

Type II Diabetes and Related Disorders: It is well established that the incretins GLP-1 and GIP are rapidly inactivated *in vivo* by DP-IV. Studies with DP-IV<sup>(-/-)</sup>-deficient mice and preliminary clinical trials indicate that DP-IV inhibition increases the steady state concentrations of GLP-1 and GIP, resulting in improved glucose tolerance. By analogy to GLP-1 and GIP, it is likely that other glucagon family peptides involved in glucose regulation are also inactivated by DP-IV (eg. PACAP, glucagon). Inactivation of these peptides by DP-IV may also play a role in glucose homeostasis. The DP-IV inhibitors of the present invention therefore have utility in the treatment of type II diabetes and in the treatment and prevention of the numerous conditions that often accompany Type II diabetes, including metabolic syndrome X, reactive hypoglycemia, and diabetic dyslipidemia. Obesity, discussed below, is another condition that is often found with Type II diabetes that may respond to treatment with the compounds of this invention.

The following diseases, disorders and conditions are related to Type 2 diabetes, and therefore may be treated, controlled or in some cases prevented, by treatment with the compounds of this invention: (1) hyperglycemia, (2) low glucose tolerance, (3) insulin resistance, (4) obesity, (5) lipid disorders, (6) dyslipidemia, (7) hyperlipidemia, (8) hypertriglyceridemia, (9) hypercholesterolemia, (10) low HDL levels, (11) high LDL levels, (12) atherosclerosis and its sequelae, (13) vascular restenosis, (14) irritable bowel syndrome, (15) inflammatory bowel disease, including Crohn's disease and ulcerative colitis, (16) other inflammatory conditions,

(17) pancreatitis, (18) abdominal obesity, (19) neurodegenerative disease, (20) retinopathy, (21) nephropathy, (22) neuropathy, (23) Syndrome X, (24) ovarian hyperandrogenism (polycystic ovarian syndrome), and other disorders where insulin resistance is a component.

- 5 Obesity: DP-IV inhibitors may be useful for the treatment of obesity. This is based on the observed inhibitory effects on food intake and gastric emptying of GLP-1 and GLP-2. Exogenous administration of GLP-1 in humans significantly decreases food intake and slows gastric emptying (Am. J. Physiol., 277: R910-R916 (1999)). ICV administration of GLP-1 in rats and mice also has profound effects on food intake (Nature Medicine, 2: 1254-1258 (1996)).
- 10 This inhibition of feeding is not observed in GLP-1R<sup>(-/-)</sup> mice, indicating that these effects are mediated through brain GLP-1 receptors. By analogy to GLP-1, it is likely that GLP-2 is also regulated by DP-IV. ICV administration of GLP-2 also inhibits food intake, analogous to the effects observed with GLP-1 (Nature Medicine, 6: 802-807 (2000)).
- 15 Growth Hormone Deficiency: DP-IV inhibition may be useful for the treatment of growth hormone deficiency, based on the hypothesis that growth-hormone releasing factor (GRF), a peptide that stimulates release of growth hormone from the anterior pituitary, is cleaved by the DP-IV enzyme *in vivo* (WO 00/56297). The following data provide evidence that GRF is an endogenous substrate: (1) GRF is efficiently cleaved *in vitro* to generate the inactive product
- 20 GRF[3-44] (BBA 1122: 147-153 (1992)); (2) GRF is rapidly degraded in plasma to GRF[3-44]; this is prevented by the DP-IV inhibitor diprotin A; and (3) GRF[3-44] is found in the plasma of a human GRF transgenic pig (J. Clin. Invest., 83: 1533-1540 (1989)). Thus DP-IV inhibitors may be useful for the same spectrum of indications which have been considered for growth hormone secretagogues.
- 25 Intestinal Injury: The potential for using DP-IV inhibitors for the treatment of intestinal injury is suggested by the results of studies indicating that glucagon-like peptide-2 (GLP-2), a likely endogenous substrate for DP-IV, may exhibit trophic effects on the intestinal epithelium (Regulatory Peptides, 90: 27-32 (2000)). Administration of GLP-2 results in increased small
- 30 bowel mass in rodents and attenuates intestinal injury in rodent models of colitis and enteritis.
- Immunosuppression: DP-IV inhibition may be useful for modulation of the immune response, based upon studies implicating the DP-IV enzyme in T cell activation and in chemokine processing, and efficacy of DP-IV inhibitors in *in vivo* models of disease. DP-IV has been shown

to be identical to CD26, a cell surface marker for activated immune cells. The expression of CD26 is regulated by the differentiation and activation status of immune cells. It is generally accepted that CD26 functions as a co-stimulatory molecule in *in vitro* models of T cell activation. A number of chemokines contain proline in the penultimate position, presumably to protect them from degradation by non-specific aminopeptidases. Many of these have been shown to be processed *in vitro* by DP-IV. In several cases (RANTES, LD78-beta, MDC, eotaxin, SDF-1alpha), cleavage results in an altered activity in chemotaxis and signaling assays. Receptor selectivity also appears to be modified in some cases (RANTES). Multiple N-terminally truncated forms of a number of chemokines have been identified in *in vitro* cell culture systems, including the predicted products of DP-IV hydrolysis.

DP-IV inhibitors have been shown to be efficacious immunosuppressants in animal models of transplantation and arthritis. Prodiptine (Pro-Pro-diphenyl-phosphonate), an irreversible inhibitor of DP-IV, was shown to double cardiac allograft survival in rats from day 7 to day 14 (Transplantation, 63: 1495-1500 (1997)). DP-IV inhibitors have been tested in collagen and alkylamine-induced arthritis in rats and showed a statistically significant attenuation of hind paw swelling in this model [Int. J. Immunopharmacology, 19:15-24 (1997) and Immunopharmacology, 40: 21-26 (1998)]. DP-IV is upregulated in a number of autoimmune diseases including rheumatoid arthritis, multiple sclerosis, Graves' disease, and Hashimoto's thyroiditis (Immunology Today, 20: 367-375 (1999)).

HIV Infection: DP-IV inhibition may be useful for the treatment or prevention of HIV infection or AIDS because a number of chemokines which inhibit HIV cell entry are potential substrates for DP-IV (Immunology Today 20: 367-375 (1999)). In the case of SDF-1alpha, cleavage decreases antiviral activity (PNAS, 95: 6331-6 (1998)). Thus, stabilization of SDF-1alpha through inhibition of DP-IV would be expected to decrease HIV infectivity.

Hematopoiesis: DP-IV inhibition may be useful for the treatment or prevention of hematopoiesis because DP-IV may be involved in hematopoiesis. A DP-IV inhibitor, Val-Boro-Pro, stimulated hematopoiesis in a mouse model of cyclophosphamide-induced neutropenia (WO 99/56753).

Neuronal Disorders: DP-IV inhibition may be useful for the treatment or prevention of various neuronal or psychiatric disorders because a number of peptides implicated in a variety of neuronal processes are cleaved *in vitro* by DP-IV. A DP-IV inhibitor thus may have a therapeutic benefit in the treatment of neuronal disorders. Endomorphin-2, beta-casomorphin,

and substance P have all been shown to be *in vitro* substrates for DP-IV. In all cases, *in vitro* cleavage is highly efficient, with  $k_{cat}/K_m \sim 10^6 \text{ M}^{-1}\text{s}^{-1}$  or greater. In an electric shock jump test model of analgesia in rats, a DP-IV inhibitor showed a significant effect that was independent of the presence of exogenous endomorphin-2 (Brain Research, 815: 278-286 (1999)).

- 5 Neuroprotective and neuroregenerative effects of DP-IV inhibitors were also evidenced by the inhibitors' ability to protect motor neurons from excitotoxic cell death, to protect striatal innervation of dopaminergic neurons when administered concurrently with MPTP, and to promote recovery of striatal innervation density when given in a therapeutic manner following MPTP treatment [see Yong-Q. Wu, et al., "Neuroprotective Effects of Inhibitors of Dipeptidyl  
10 Peptidase-IV In Vitro and In Vivo," Int. Conf. On Dipeptidyl Aminopeptidases: Basic Science and Clinical Applications, September 26-29, 2002 (Berlin, Germany)].

- Tumor Invasion and Metastasis: DP-IV inhibition may be useful for the treatment or prevention of tumor invasion and metastasis because an increase or decrease in expression of several  
15 ectopeptidases including DP-IV has been observed during the transformation of normal cells to a malignant phenotype (J. Exp. Med., 190: 301-305 (1999)). Up- or down-regulation of these proteins appears to be tissue and cell-type specific. For example, increased CD26/DP-IV expression has been observed on T cell lymphoma, T cell acute lymphoblastic leukemia, cell-derived thyroid carcinomas, basal cell carcinomas, and breast carcinomas. Thus, DP-IV  
20 inhibitors may have utility in the treatment of such carcinomas.

- Benign Prostatic Hypertrophy: DP-IV inhibition may be useful for the treatment of benign prostatic hypertrophy because increased DP-IV activity was noted in prostate tissue from patients with BPH (Eur. J. Clin. Chem. Clin. Biochem., 30: 333-338 (1992)).

- 25 Sperm motility/male contraception: DP-IV inhibition may be useful for the altering sperm motility and for male contraception because in seminal fluid, prostatesomes, prostate derived organelles important for sperm motility, possess very high levels of DP-IV activity (Eur. J. Clin. Chem. Clin. Biochem., 30: 333-338 (1992)).

- 30 Gingivitis: DP-IV inhibition may be useful for the treatment of gingivitis because DP-IV activity was found in gingival crevicular fluid and in some studies correlated with periodontal disease severity (Arch. Oral Biol., 37: 167-173 (1992)).



Osteoporosis: DP-IV inhibition may be useful for the treatment or prevention of osteoporosis because GIP receptors are present in osteoblasts.

The compounds of the present invention have utility in treating or preventing one or more of the following conditions or diseases: (1) hyperglycemia, (2) low glucose tolerance, (3) insulin resistance, (4) obesity, (5) lipid disorders, (6) dyslipidemia, (7) hyperlipidemia, (8) hypertriglyceridemia, (9) hypercholesterolemia, (10) low HDL levels, (11) high LDL levels, (12) atherosclerosis and its sequelae, (13) vascular restenosis, (14) irritable bowel syndrome, (15) inflammatory bowel disease, including Crohn's disease and ulcerative colitis, (16) other inflammatory conditions, (17) pancreatitis, (18) abdominal obesity, (19) neurodegenerative disease, (20) retinopathy, (21) nephropathy, (22) neuropathy, (23) Syndrome X, (24) ovarian hyperandrogenism (polycystic ovarian syndrome), (25) Type II diabetes, (26) growth hormone deficiency, (27) neutropenia, (28) neuronal disorders, (29) tumor metastasis, (30) benign prostatic hypertrophy, (32) gingivitis, (33) hypertension, (34) osteoporosis, and other conditions that may be treated or prevented by inhibition of DP-IV.

The subject compounds are further useful in a method for the prevention or treatment of the aforementioned diseases, disorders and conditions in combination with other agents.

The compounds of the present invention may be used in combination with one or more other drugs in the treatment, prevention, suppression or amelioration of diseases or conditions for which compounds of Formula I or the other drugs may have utility, where the combination of the drugs together are safer or more effective than either drug alone. Such other drug(s) may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of Formula I. When a compound of Formula I is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such other drugs and the compound of Formula I is preferred. However, the combination therapy may also include therapies in which the compound of Formula I and one or more other drugs are administered on different overlapping schedules. It is also contemplated that when used in combination with one or more other active ingredients, the compounds of the present invention and the other active ingredients may be used in lower doses than when each is used singly. Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more other active ingredients, in addition to a compound of Formula I.

Examples of other active ingredients that may be administered in combination with a compound of Formula I, and either administered separately or in the same pharmaceutical composition, include, but are not limited to:

- (a) other dipeptidyl peptidase IV (DP-IV) inhibitors;
- 5 (b) insulin sensitizers including (i) PPAR $\gamma$  agonists such as the glitazones (e.g. troglitazone, pioglitazone, englitazone, MCC-555, rosiglitazone, and the like) and other PPAR ligands, including PPAR $\alpha/\gamma$  dual agonists, such as KRP-297, and PPAR $\alpha$  agonists such as fenofibric acid derivatives (gemfibrozil, clofibrate, fenofibrate and bezafibrate), (ii) biguanides such as metformin and phenformin, and (iii) protein tyrosine phosphatase-1B (PTP-1B)  
10 inhibitors;
- (c) insulin or insulin mimetics;
- (d) sulfonylureas and other insulin secretagogues, such as tolbutamide, glyburide, glipizide, glimepiride, and meglitinides, such as repaglinide;
- (e)  $\alpha$ -glucosidase inhibitors (such as acarbose and miglitol);
- 15 (f) glucagon receptor antagonists such as those disclosed in WO 98/04528, WO 99/01423, WO 00/39088, and WO 00/69810;
- (g) GLP-1, GLP-1 mimetics, and GLP-1 receptor agonists such as those disclosed in WO00/42026 and WO00/59887;
- (h) GIP and GIP mimetics such as those disclosed in WO00/58360, and GIP  
20 receptor agonists;
- (i) PACAP, PACAP mimetics, and PACAP receptor agonists such as those disclosed in WO 01/23420;
- (j) cholesterol lowering agents such as (i) HMG-CoA reductase inhibitors (lovastatin, simvastatin, pravastatin, cerivastatin, fluvastatin, atorvastatin, itavastatin, and  
25 rosuvastatin, and other statins), (ii) sequestrants (cholestyramine, colestipol, and dialkylaminoalkyl derivatives of a cross-linked dextran), (iii) nicotiny alcohol, nicotinic acid or a salt thereof, (iv) PPAR $\alpha$  agonists such as fenofibric acid derivatives (gemfibrozil, clofibrate, fenofibrate and bezafibrate), (v) PPAR $\alpha/\gamma$  dual agonists, such as KRP-297, (vi) inhibitors of cholesterol absorption, such as beta-sitosterol and ezetimibe, (vii) acyl CoA:cholesterol  
30 acyltransferase inhibitors, such as avasimibe, and (viii) anti-oxidants, such as probucol;
- (k) PPAR $\delta$  agonists, such as those disclosed in WO97/28149;
- (l) antiobesity compounds such as fenfluramine, dexfenfluramine, phentermine, sibutramine, orlistat, neuropeptide Y5 inhibitors, CB-1 antagonists, MC-4R agonists, and  $\beta_3$  adrenergic receptor agonists;

(m) an ileal bile acid transporter inhibitor;

(n) agents intended for use in inflammatory conditions such as aspirin, non-steroidal anti-inflammatory drugs, glucocorticoids, azulfidine, and selective cyclooxygenase-2 inhibitors; and

5 (o) antihypertensive agents such as ACE inhibitors (enalapril, lisinopril, captopril, quinapril, tandolapril), A-II receptor blockers (losartan, candesartan, irbesartan, valsartan, telmisartan, eprosartan), beta blockers and calcium channel blockers.

The above combinations include combinations of a compound of the present invention not only with one other active compound, but also with two or more other active  
10 compounds. Non-limiting examples include combinations of compounds having Formula I with two or more active compounds selected from biguanides, sulfonylureas, HMG-CoA reductase inhibitors, PPAR agonists, PTP-1B inhibitors, other DP-IV inhibitors, and anti-obesity compounds.

Likewise, compounds of the present invention may be used in combination with  
15 other drugs that are used in the treatment/prevention/suppression or amelioration of the diseases or conditions for which compounds of the present invention are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical  
20 composition containing such other drugs in addition to the compound of the present invention is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of the present invention.

The weight ratio of the compound of the compound of the present invention to the  
25 second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with another agent, the weight ratio of the compound of the present invention to the other agent will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the  
30 present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

The compounds of the present invention may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), by inhalation spray, nasal, vaginal, rectal, sublingual, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, monkeys, etc., the compounds of the invention are effective for use in humans.

The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract

and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Patents 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

5                   Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

10                   Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy- propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation  
15 products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also  
20 contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

                  Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such  
25 as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

                  Dispersible powders and granules suitable for preparation of an aqueous  
30 suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally- occurring gums, for example gum acacia or gum tragacanth, naturally-  
5 occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example  
10 glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been  
15 mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed  
20 oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of the present invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by  
25 mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of The present invention are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

30 The pharmaceutical composition and method of the present invention may further comprise other therapeutically active compounds as noted herein which are usually applied in the treatment of the above mentioned pathological conditions.

In the treatment or prevention of conditions which require inhibition of dipeptidyl peptidase-IV enzyme activity an appropriate dosage level will generally be about 0.01 to 500 mg

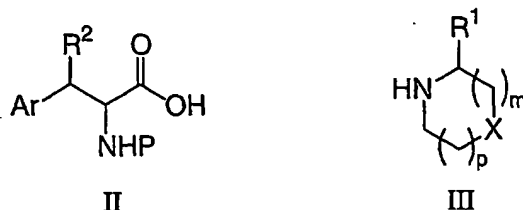
per kg patient body weight per day which can be administered in single or multiple doses. Preferably, the dosage level will be about 0.1 to about 250 mg/kg per day; more preferably about 0.5 to about 100 mg/kg per day. A suitable dosage level may be about 0.01 to 250 mg/kg per day, about 0.05 to 100 mg/kg per day, or about 0.1 to 50 mg/kg per day. Within this range the dosage may be 0.05 to 0.5, 0.5 to 5 or 5 to 50 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 mg of the active ingredient, particularly 1.0, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 mg of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

When treating or preventing diabetes mellitus and/or hyperglycemia or hypertriglyceridemia or other diseases for which compounds of the present invention are indicated, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.1 mg to about 100 mg per kilogram of animal body weight, preferably given as a single daily dose or in divided doses two to six times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 1.0 mg to about 1000 mg, preferably from about 1 mg to about 50 mg. In the case of a 70 kg adult human, the total daily dose will generally be from about 7 mg to about 350 mg. This dosage regimen may be adjusted to provide the optimal therapeutic response.

It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

Several methods for preparing the compounds of this invention are illustrated in the following Schemes and Examples. Starting materials are made according to procedures known in the art or as illustrated herein.

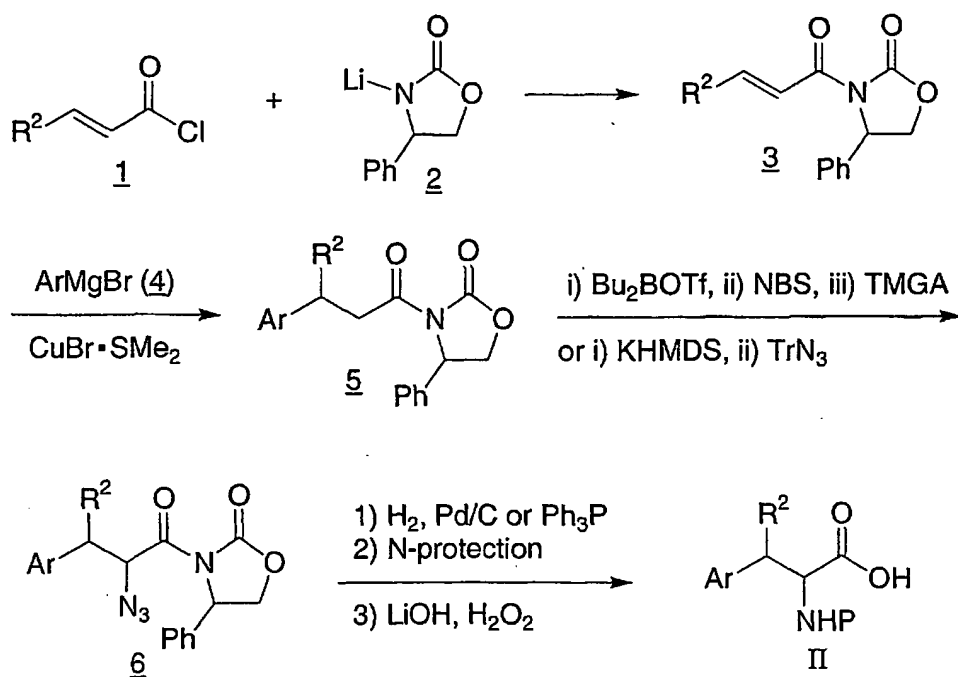
The compounds of the present invention can be prepared from alpha amino acid intermediates such as those of formula II and substituted heterocyclic intermediates such as those of formula III, using standard peptide coupling conditions followed by deprotection. The preparation of these intermediates is described in the following Schemes,



wherein m, p, Ar, X, R<sup>1</sup>, and R<sup>2</sup> are as defined above and P is a suitable nitrogen protecting group such as tert-butoxycarbonyl (BOC), benzyloxycarbonyl (Cbz), or 9-fluorenylmethoxycarbonyl (Fmoc).

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### SCHEME 1

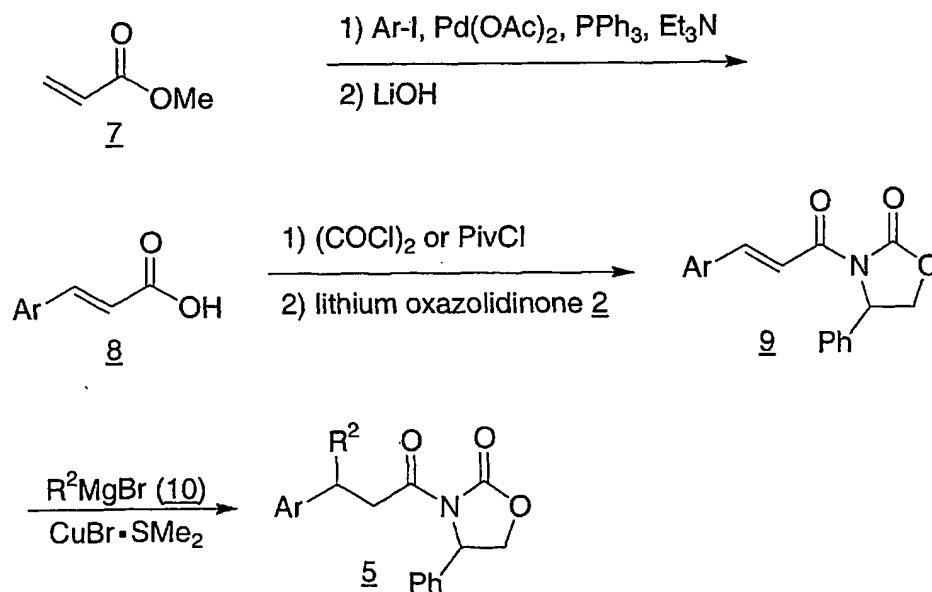


Compounds of formula II are commercially available, known in the literature or may be conveniently prepared by a variety of methods familiar to those skilled in the art. One convenient route described in the literature (X. Qian *et al.*, *Tetrahedron*, 51: 1033-1054 (1995)) is illustrated in Scheme 1. An activated acid derivative such as acid chloride **1**, which may be commercially available or readily prepared from the corresponding acid, for example, by treatment with thionyl chloride or oxalyl chloride, is treated the lithium anion of phenyloxazolidinone **2** to provide acyl oxazolidinone **3**. Conjugate addition of the appropriate



aryl Grignard reagent 4 to oxazolidinone 3 provides intermediate 5. An alpha-azido moiety may be introduced in one of two convenient ways. First, the boron enolate generated from acyl oxazolidinone 5 by treatment with boron triflate and a base such as triethylamine or diisopropylethylamine is brominated by reaction with *N*-bromosuccinimide. The resultant  
 5 bromide is displaced with azide, for example, by treatment with tetramethylguanidinium azide to provide azide 6. Alternatively, the potassium enolate of acyl oxazolidinone 5, generated for example with potassium hexamethyldisilazide, may be reacted with 2,4,6-triisopropylbenzenesulfonyl azide (trisyl azide) to provide azide 6 directly. The azide is reduced  
 10 by catalytic hydrogenation or by treatment with triphenylphosphine and the resultant amine protected with an appropriate group, for example, as its *N*-tert-butyloxycarbonyl (Boc) derivative by treatment with di-*tert*-butyldicarbonate. The oxazolidinone is hydrolyzed, conveniently by treatment with lithium hydroperoxide, to provide the desired acid intermediate II. As will be readily apparent to those skilled in the art, all four diastereomers of acid II are available in  
 15 enantiomerically pure form via this route, through the appropriate selection of either the (*R*) or (*S*) enantiomer of oxazolidinone 2 and employing the appropriate method for conversion of acyl oxazolidinone 5 to azide 6.

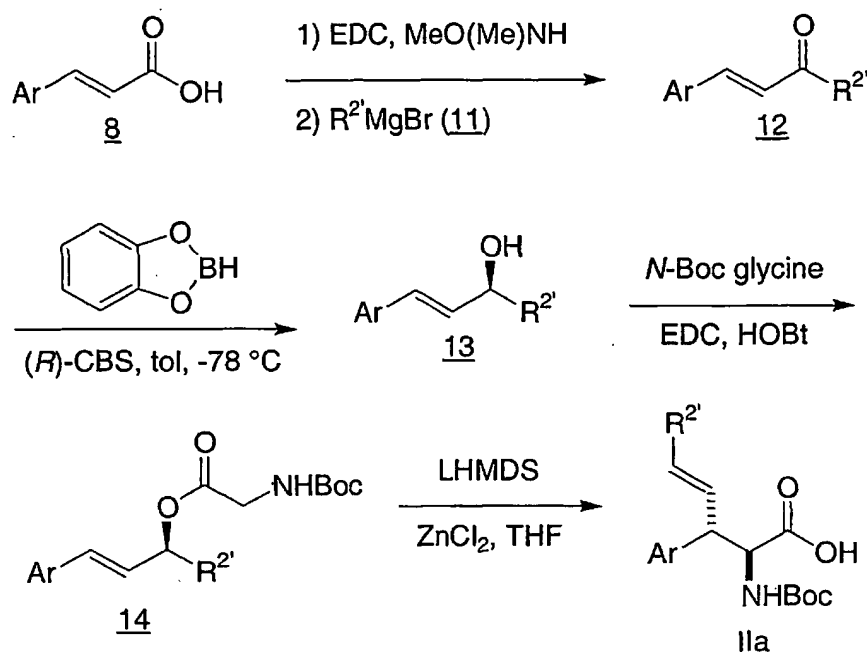
## SCHEME 2



The aryl and R<sup>2</sup> substituent in intermediate 5 may be introduced in the reverse order, as illustrated in Scheme 2. Acid 8 is commercially available or readily prepared by a variety of methods known to those skilled in the art. In one such method, methyl acrylate (7) is treated with an aryl iodide under Stille coupling conditions to provide acid 8, after hydrolysis of the ester. Activation of the acid, for example as its acid chloride by treatment with oxalyl chloride or as a mixed anhydride by reaction with pivaloyl chloride, followed by treatment with lithium oxazolidinone 2 gives acyl oxazolidinone 9. Copper catalyzed addition of the appropriate Grignard reagent 10 gives the desired intermediate 5. Conversion to intermediate II may be carried out as described in Scheme 1.

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## SCHEME 3

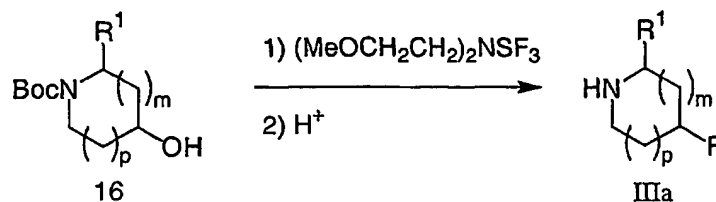


An alternate method for the preparation of intermediate II wherein R<sup>2</sup> contains an optionally substituted vinyl group, and R<sup>2</sup> and the protected amine are anti to each other is shown in Scheme 3. Acid 8 may undergo EDC-mediated coupling to *N,O*-dimethylhydroxylamine followed by treatment with the appropriate Grignard reagent 11 to provide ketone 12. Reduction to alcohol 13 may be achieved in an asymmetric fashion by treatment with catecholborane in the presence of, for example, the (*R*) isomer of the CBS catalyst. The alcohol is coupled to *N*-Boc glycine to provide ester 14. [3,3]-Sigmatropic rearrangement of the enolate of ester 14 may be

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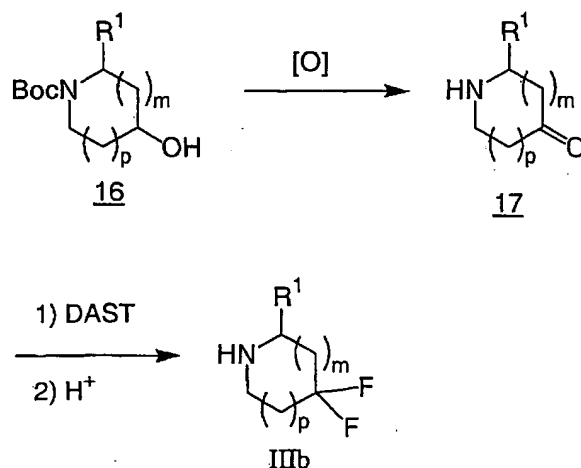
achieved as described by U. Kazmaier in *Angew. Chem. Int. Ed. Eng.* 33: 998-999 (1994) to provide intermediate IIa.

#### SCHEME 4



Compounds of formula **III** are commercially available, known in the literature or may be conveniently prepared by a variety of methods familiar to those skilled in the art. One convenient method for the preparation of intermediate **III** wherein X is CHF is shown in Scheme 4. An appropriately protected alcohol **16**, which itself is known in the literature or may be conveniently prepared by a variety of methods familiar to those skilled in the art, is treated with a fluorinating reagent such as (diethylamino)sulfur trifluoride (DAST) or [bis(2-methoxyethyl)amino]sulfur trifluoride to provide, after deprotection, the fluoro intermediate **IIIa**.

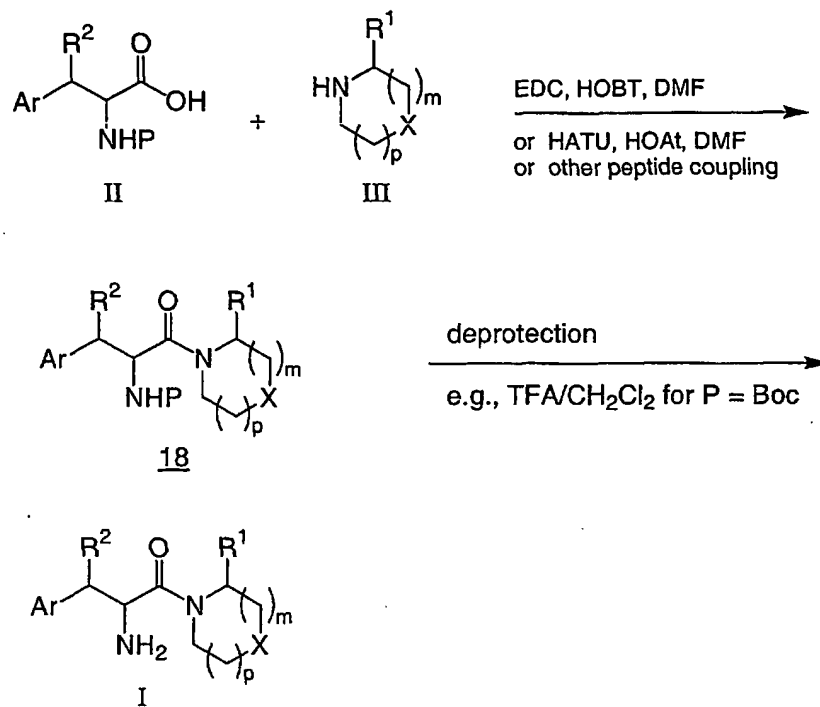
#### SCHEME 5



A method for the preparation of intermediate **III** wherein X is  $\text{CF}_2$  is shown in Scheme 5. An appropriately protected alcohol **16** is oxidized to the corresponding ketone **17** by

a variety of methods known to those skilled in the art. Ketone 17 is treated with a fluorinating reagent such as DAST to provide, after deprotection, the difluoro intermediate IIIb.

SCHEME 6



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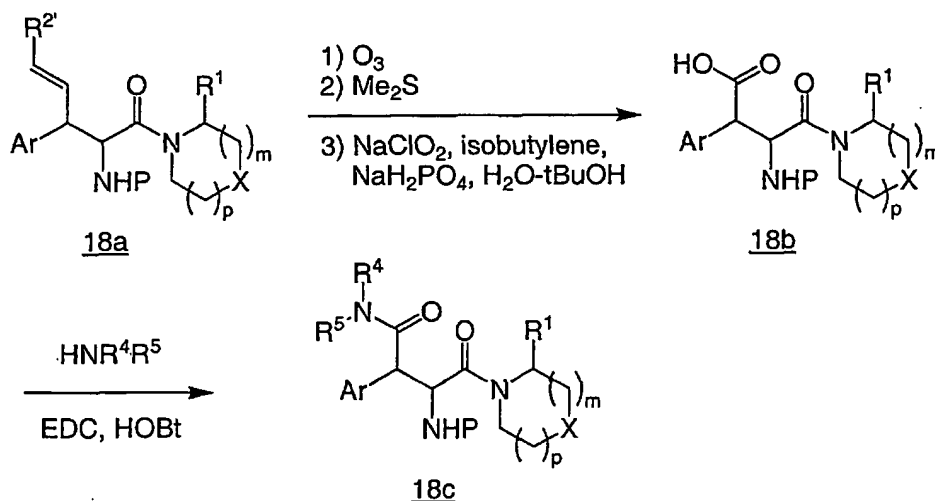
Intermediates II and III are coupled under standard peptide coupling conditions, for example, using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide and 1-hydroxybenzotriazole (EDC/HOBT) or *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate and 1-hydroxy-7-azabenzotriazole (HATU/HOAT) in a solvent such as N,N-dimethylformamide (DMF) or dichloromethane for 3 to 48 h at ambient temperature to provide Intermediate 18 as shown in Scheme 6. In some cases, Intermediate III may be a salt, such as a hydrochloride or trifluoroacetic acid salt, and in these cases it is convenient to add a base, generally diisopropylethylamine, to the coupling reaction. The protecting group is then removed with, for example, trifluoroacetic acid or methanolic hydrogen chloride in the case of Boc to give the desired amine I. The product is purified from unwanted side products, if necessary, by recrystallization, trituration, preparative thin layer chromatography, flash chromatography on silica gel, such as with a Biotage® apparatus, or HPLC. Compounds that are

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purified by HPLC may be isolated as the corresponding salt. Purification of intermediates is achieved in the same manner.

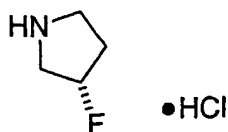
In some cases the product I, prepared as described in Scheme 6, may be further modified, for example, by manipulation of substituents on Ar or R<sup>2</sup>. These manipulations may include, but are not limited to, reduction, oxidation, alkylation, acylation, and hydrolysis reactions which are commonly known to those skilled in the art.

### SCHEME 7



In some cases intermediates described in the above schemes may be further modified before the sequences are completed, for example, by manipulation of substituents on Ar or R<sup>2</sup>. These manipulations may include, but are not limited to, reduction, oxidation, alkylation, acylation, and hydrolysis reactions which are commonly known to those skilled in the art. One such example is illustrated in Scheme 7. Ozonolysis of intermediate **18a**, wherein R<sup>2</sup> is an optionally substituted vinyl group, followed by oxidation provides acid **18b**. The acid may be coupled with an amide to give amide **18c**. Both **18b** and **18c** may be converted to a compound of formula I as illustrated in Scheme 6.

In some cases the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products. The following examples are provided so that the invention might be more fully understood. These examples are illustrative only and should not be construed as limiting the invention in any way.

INTERMEDIATE 1(3S)-3-Fluoropyrrolidine hydrochloride5    Step A:        Benzyl (3R)-3-hydroxypyrrolidine-1-carboxylate

A 22-L, 3-neck, round bottom flask equipped with mechanical stirrer, thermocouple, addition funnel and nitrogen bubbler was charged with 425 g (4.88 mol) of (3R)-3-hydroxypyrrolidine, 8 L of dichloromethane, and 1 L (7.17 mol) of triethylamine. The solution was cooled to 5 – 10 °C with an ice bath and then 1000 g (5.86 mol) of benzyl chloroformate was added dropwise over a period of about 1.5 h keeping the reaction temperature below 20 °C. The reaction mixture was stirred for an additional h in the ice bath, then the bath was removed and the reaction mixture was allowed to warm to ambient temperature overnight. The mixture was poured into a large extractor containing about 15 L of saturated aqueous sodium bicarbonate solution. The aqueous phase was back-extracted with two 2-L portions of dichloromethane. The combined organics were dried over magnesium sulfate and concentrated to give an orange oil. The crude material was taken up in dichloromethane, applied to a 5-kg column of silica gel prepacked in 50% ethyl acetate/hexane, and eluted sequentially with 8 L of 50%, 16 L of 75%, then 100% ethyl acetate/hexane to provide the title compound as a yellow oil which crystallized upon standing.

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Step B:        Benzyl (3S)-3-fluoropyrrolidine-1-carboxylate

A 5-L, 3-neck, round bottom flask equipped with mechanical stirrer, thermocouple, addition funnel and nitrogen bubbler was charged with 375 mL (2.84 mol) of (diethylamino)sulfur trifluoride and 400 mL of dichloromethane. The solution was cooled to –78 °C. To this was added via addition funnel a solution of 304 g (1.37 mol) of benzyl (3R)-3-hydroxypyrrolidine-1-carboxylate in 400 mL of dichloromethane over a 2-h period keeping the reaction temperature below –70 °C. The reaction mixture was allowed to stir and warm slowly to ambient temperature overnight. The reaction mixture was added portion-wise with caution to a large extractor containing ice, water, and saturated aqueous sodium bicarbonate solution. The mixture was extracted with 8 L of ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated to give a brown oil. Purification by flash

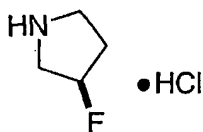
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chromatography (silica gel, eluting with a 10 to 30% ethyl acetate/hexane gradient) gave the title compound as a brown oil.

Step C: (3S)-3-Fluoropyrrolidine hydrochloride

- 5           Benzyl (3S)-3-fluoropyrrolidine-1-carboxylate (249 g, 1.11 mmol) was dissolved in 2.3 L of ethanol and then 115 mL of water was added, followed by 30 g of 10% palladium on carbon. The mixture was shaken under 40 psi hydrogen for ~24 h. An additional 10 g and then 5 g of catalyst were added. The mixture was stirred under 40 psi hydrogen until complete. The mixture was filtered and the filter cake washed with ethanol. The combined filtrate and
- 10 washings were treated with 185 mL of concentrated hydrochloric acid and concentrated to a colorless oil. The residue was azeotroped with toluene, then 2 L of diethyl ether were added. Isopropyl alcohol was added until the the oil crystallized. The mixture was allowed to age at ambient temperature over the weekend. The crystals were collected, washed with diethyl ether, and dried in vacuo to give the title compound. The mother liquors and washings were combined,
- 15 concentrated, azeotroped with toluene, and triturated with diethyl ether/isopropyl alcohol. The second crop was collected and dried in vacuo to give additional title compound.  $[\alpha]_D^{25} = +8.64^\circ$  ( $c = 4$ , methanol).

INTERMEDIATE 2



20

(3R)-3-Fluoropyrrolidine hydrochloride

Step A: Benzyl (3S)-3-Acetoxypyrrolidine-1-carboxylate

- 25           A 22-L, 3 neck round bottom flask equipped with a mechanical stirrer, thermocouple, addition funnel and nitrogen bubbler was charged with 422 g (1.91 mol) of benzyl (3R)-3-hydroxypyrrolidine-1-carboxylate (Intermediate 1, Step A), 12 L of toluene, 751 g (2.86 mol) of triphenylphosphine, and 164 mL (2.86 mol) of glacial acetic acid. The resultant mixture was stirred at ambient temperature and then 500 g (2.87 mol) of diethyl azodicarboxylate was added via the addition funnel over a period of about 30 min, keeping the internal temperature
- 30 below 28 °C with a cold water bath. The reaction was stirred at ambient temperature overnight. The solvent was removed in vacuo and the residue was triturated with 6 L of diethyl ether. The

solid was filtered off and washed well with diethyl ether. The filtrate and ether washings were combined and concentrated to a thick yellow oil with solids. Purification by flash chromatography (silica gel, eluting sequentially with 5% and a gradient of 10% to 30% ethyl acetate/hexane) gave the title compound as a pale yellow oil.

5

Step B: Benzyl (3S)-3-hydroxypyrrolidine-1-carboxylate

To a 20-L, three neck round bottom flask containing 427 g (1.62 mol) of benzyl (3S)-3-acetoxypyrrolidine-1-carboxylate was added 4 L of absolute ethanol followed by 101 g (1.57 mol) of potassium hydroxide in about 400 mL of water. After about 15 min, the reaction mixture was poured into 8 L of water and extracted with 8 L of ethyl acetate. The aqueous layer was then extracted with an additional 4 L of ethyl acetate. The combined organics were washed with brine, dried over magnesium sulfate and concentrated to a thick oil and solids.

15

Step C: Benzyl (3R)-3-fluoropyrrolidine-1-carboxylate

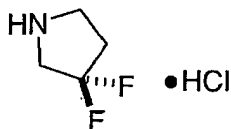
A 366 g (1.62 mol) portion of benzyl (3S)-3-hydroxypyrrolidine-1-carboxylate was converted to the title compound essentially following the procedure outlined in Intermediate 1, Step B.

20

Step D: (3R)-3-Fluoropyrrolidine hydrochloride

A 222 g (1.0 mol) portion of benzyl (3R)-3-fluoropyrrolidine-1-carboxylate was converted to the title compound essentially following the procedure outlined in Intermediate 1, Step C.  $[\alpha]_D = -8.61$  ( $c = 4$ , methanol).

INTERMEDIATE 3



25

3,3-Difluoropyrrolidine hydrochloride

Step A: Benzyl 3-oxopyrrolidine-1-carboxylate

A 12-L, 3 neck round bottom flask equipped with a mechanical stirrer, thermocouple, condenser, and nitrogen bubbler was charged with 351 g (1.61 mol) of benzyl (3R)-3-hydroxypyrrolidine-1-carboxylate (Intermediate 1, Step A), 6 L of dichloromethane, 500



g of powdered molecular sieves, and 400 g (3.41 mol) of *N*-methyilmorpholine-*N*-oxide. The resultant suspension was stirred at ambient temperature and to this was added 12.9 g (0.0367 mol) of tetrapropylammonium perruthenate. The reaction temperature was kept at or below 30 °C with a cold water bath. The mixture was stirred at ambient temperature for 2 h. The mixture was poured onto a plug of 5 kg of silica gel and eluted with 10% ethyl acetate/dichloromethane to give the title compound as an orange oil.

Step B: Benzyl 3,3-difluoropyrrolidine-1-carboxylate

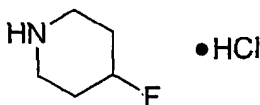
A 12-L, 3 neck round bottom flask equipped with a mechanical stirrer, thermocouple, addition funnel and nitrogen bubbler was charged with 292 g (1.33 mol) of benzyl 3-oxopyrrolidine-1-carboxylate and 3 L of dichloromethane. To the stirring solution at ambient temperature was added dropwise 530 mL (4.0 mol) of (diethylamino)sulfur trifluoride over a period of about 3 h, keeping the internal temperature less than 25 °C using a cold water bath. The mixture was stirred at ambient temperature overnight. The mixture was poured into a large extractor containing ice and solid sodium bicarbonate. Eight liters of ethyl acetate were then added and the mixture was made basic with sodium bicarbonate. Layers were separated. The organics were dried over magnesium sulfate and concentrated to 309 g of a brown oil. Purification by flash chromatography (silica gel, 10 to 20% ethyl acetate/hexane gradient) gave the title compound.

Step C: 3,3-Difluoropyrrolidine hydrochloride

A 242 g (1.00 mol) portion of benzyl 3,3-difluoropyrrolidine-1-carboxylate was converted to the title compound essentially following the procedure outlined in Intermediate 1, Step C.

<sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD): δ 3.7 (t, 2H), 3.6 (t, 2H), 2.55 (m, 2H).

INTERMEDIATE 4



4-Fluoropiperidine hydrochloride

Step A: Benzyl 4-fluoro-1-piperidinecarboxylate

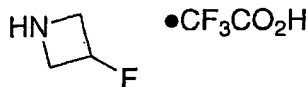
A 1-L, round bottom flask was charged with 12.64 g (51.4 mmol) of benzyl 4-oxo-1-piperidinecarboxylate and 300 mL of dichloromethane. To the stirring solution at  $-78^{\circ}\text{C}$  was added 19 mL (102.8 mmol) of [bis(2-methoxyethyl)amino]sulfur trifluoride via addition funnel over a period of about 1 h. The reaction mixture was allowed to warm slowly to ambient temperature overnight. The reaction mixture was added portionwise with caution to a large extractor containing water and saturated aqueous sodium bicarbonate solution. The mixture was extracted with dichloromethane (3 x 300 mL). The combined organic layers were washed once with saturated aqueous sodium bicarbonate solution, twice with 10% aqueous hydrochloric acid solution and brine, dried over sodium sulfate, and concentrated *in vacuo*. Purification by flash chromatography on a Biotage® system (gradient, hexane to 65% ethyl acetate/hexane) afforded the desired product. LC/MS 242.1 (M+1).

Step B: 4-Fluoropiperidine hydrochloride

Benzyl 4-fluoro-1-piperidinecarboxylate (5.5 g, 23.2 mmol) was dissolved in 80 mL of ethanol and 1.0 g of 20% palladium hydroxide (dry basis) on carbon was added to the mixture. The mixture was shaken under 40 psi hydrogen for about 12 h then filtered through a celite pad and washed with 100 mL of methanol. The combined filtrate and washings were treated with 60 mL of 1 M hydrochloric acid in diethyl ether and concentrated to a white waxy solid. The solid was dried *in vacuo* to give the title compound as a solid with a minor unidentified impurity. The material was used without further purification.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  4.95 (d,  $J = 47.4$  Hz, 1 H), 3.70 (br s, 1 H), 3.34-3.27 (m, 4 H), 2.29 (dt,  $J = 37.1, 12.3$  Hz, 2 H), 2.16 (br s, 2 H).

INTERMEDIATE 5



3-Fluoroazetidine trifluoroacetic acid salt

Step A: 1-Benzhydryl-3-fluoroazetidine

A 250 mL, round bottom flask was charged with 3.0 g (12.5 mmol) of 1-benzhydryl-3-hydroxyazetidine and 80 mL of dichloromethane. To the stirring solution at  $-78^{\circ}\text{C}$  was added 4.6 mL (25 mmol) of [bis(2-methoxyethyl)amino]sulfur trifluoride via addition funnel over a period of about 3 h. The reaction mixture was allowed to warm slowly to ambient

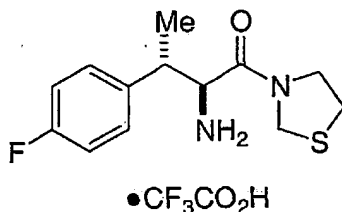
temperature overnight. The reaction mixture was added portionwise (with caution) to a large extractor containing water and saturated aqueous sodium bicarbonate solution. The mixture was extracted three times with 80 mL of dichloromethane. The combined organic layers were washed sequentially with saturated aqueous sodium bicarbonate solution, water and brine, dried over sodium sulfate, and concentrated *in vacuo*. Purification by flash chromatography using a Biotage® system (gradient, hexane to 80% ethyl acetate/hexane) afforded the desired product. LC/MS 242.1 (M+1).

Step B: 3-Fluoroazetidine trifluoroacetic acid salt

1-Benzhydryl-3-fluoroazetidine (1.7 g, 7.04 mmol) was dissolved in 60 mL of ethanol and 500 mg of 20% palladium hydroxide (dry basis) on carbon. The mixture was shaken under 40 psi hydrogen gas for about 12 h. The mixture was filtered through a celite pad and the filter cake washed with 100 mL of methanol. The combined washings were treated with 10 mL of trifluoroacetic acid and concentrated to give two oils, the more dense of which is the desired fluoroazetidine salt. The mixture was not purified further.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 5.45-4.30 (dm, J = 56.7 Hz, 1 H), 4.46-4.38 (m, 2 H), 4.24-2.17 (m, 2 H).

EXAMPLE 1



3-[(2S,3S)-2-Amino-3-(4-fluorophenyl)-1-oxobutan-1-yl]thiazolidine, trifluoroacetic acid salt

Step A: (4S)-3-[(2E)-But-2-enoyl]-4-phenyl-1,3-oxazolidin-2-one

To a stirred solution of 4(S)-4-phenyl-2-oxazolidinone (97.0 g, 43.0 mmol) in tetrahydrofuran (THF, 100 mL) was added *n*-butyllithium (30.0 mL, 1.6M in hexanes, 48.0 mmol) at -78 °C. The mixture was stirred for 20 min and then crotonyl chloride (5.0 g, 43.0 mmol) was added. The resultant solution was stirred for 30 min at -78 °C and 1.5 h at room temperature. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution. The resultant aqueous slurry was diluted with water and extracted with three portions of ethyl acetate. The combined organic layers were washed with saturated aqueous

sodium bicarbonate solution and brine, dried over sodium sulfate, and concentrated in vacuo. Purification by flash chromatography (silica gel, 83:17 hexanes/ethyl acetate) afforded the desired product.

5    Step B:            (4S)-3-[(3R)-3-(4-Fluorophenyl)butanoyl]-4-phenyl-1,3-oxazolidin-2-one

To a stirred solution of copper(II)bromide dimethylsulfide complex (6.85 g, 33.3 mmol) in anhydrous THF (60 mL) and dimethylsulfide (30 mL) was added 4-fluorophenylmagnesium bromide (30.0 mL, 1.0 M in THF, 30.0 mmol) at -40 °C. The resultant mixture was stirred at -40 °C for 30 min, then warmed to -10 °C. The product from Step A (1.18g, 5.10 mmol) in THF (30 mL) was added to the above reaction mixture over 1 h at -10 °C. The resultant mixture was stirred at -10 °C for 2 h, then slowly warmed to room temperature and stirred at room temperature for 12 h. The reaction was quenched by slow addition of saturated aqueous ammonium chloride solution. The organic phase was separated and the aqueous phase was extracted with two portions of ethyl acetate. The combined organic layers were washed with brine and concentrated in vacuo. Purification by flash chromatography (silica gel, 80:20 hexanes/ethyl acetate) afforded the desired product.

15    Step C:            (4S)-3-[(2S,3S)-2-Azido-3-(4-fluorophenyl)butanoyl]-4-phenyl-1,3-oxazolidin-2-one

20            To a stirred solution of the product from Step B (1.18 g, 3.61 mmol) in anhydrous THF (40 mL) was added potassium hexamethyldisilazide (8.7 mL, 0.5M in toluene, 4.35 mmol) at -78 °C. The resultant mixture was stirred at -78 °C for 30 min. A precooled solution of trisyl azide (1.56 g, 5.04 mmol) in THF (30 mL) was added via cannula. After 1.5 min the reaction was quenched with glacial acetic acid (0.95 mL, 16.6 mmol) and potassium acetate (1.77 g, 18.1 mmol). The cooling bath was removed, and the reaction was stirred at room temperature for 12 h. The solution was partitioned between ethyl acetate and brine. The aqueous phase was extracted with three portions of ethyl acetate. The organic phases were combined, washed with saturated aqueous sodium bicarbonate solution, dried over sodium sulfate, and evaporated in vacuo. Purification by flash chromatography (silica gel, 80:20 hexanes/ethyl acetate) afforded the desired product.

25    Step D:            (2S,3S)-2-Azido-3-(4-fluorophenyl)butanoic acid

To a stirred solution of the product from Step C (0.88 g, 2.39 mmol) in THF (30 mL) was added water (10 mL). The solution was stirred at 0 °C for 15 min, and then 30%

hydrogen peroxide (1.60 mL, 14.3 mmol) was added followed by slow addition of lithium hydroxide (0.17 g, 7.23 mmol). The resultant mixture was stirred at 0 °C for 4 h. The reaction was quenched by addition of saturated aqueous sodium sulfite solution and stirred at room temperature for 30 min. The aqueous phase was separated and extracted with three portions of dichloromethane. The aqueous phase was then acidified to pH 1 with 3N hydrochloric acid and extracted with three portions of ethyl acetate. The ethyl acetate extracts were combined, dried over sodium sulfate, and evaporated in vacuo to give the product, which was used in the next step directly. LC/MS 224.1 (M+1).

10 Step E:      (βS)-N-(tert-Butoxycarbonyl)-4-fluoro-β-methyl-L-phenylalanine

To 500 mg (2.24 mmol) of the azide from Step D dissolved in 15 mL of 10:8:1 methanol/tetrahydrofuran/trifluoroacetic acid was added 50 mg of 10% palladium on carbon. The reaction flask was flushed with nitrogen and then stirred under a hydrogen atmosphere (1 atm) for 12 h. The reaction was passed through a pad of Celite. The filter cake was then washed with methanol, and the solvent was removed in vacuo to yield a yellow-colored foam. To this foam was added 5 mL of dioxane and 5 mL of saturated aqueous sodium bicarbonate solution followed by 1.47 g of di-*tert*-butyl dicarbonate (6.70 mmol). The reaction was stirred at room temperature for 12 h. The reaction mixture was diluted with ethyl acetate and acidified to pH 1 with 1N aqueous hydrochloric acid. The layers were separated, and aqueous layer was extracted with two portions of ethyl acetate. The organic extracts were combined, washed with brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 95:5 dichloromethane/methanol) to give the desired product. LC/MS 298.0 (M+1)

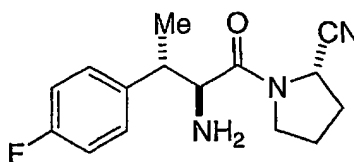
25 Step F:      3-[(2S,3S)-2-[(tert-Butoxycarbonyl)amino]-3-(4-fluorophenyl)-1-oxobutanyl]thiazolidine

To a stirred solution of the product from Step D (0.19 g, 0.65 mmol) in anhydrous dimethylformamide (DMF, 2 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 0.19 g, 0.99 mmol), hydroxybenzotriazole (HOBT, 0.13 g, 0.96 mmol), thiazolidine (0.26 mL, 3.3 mmol) and *N,N'*-diisopropylethylamine (0.33 mL, 1.9 mmol). After stirring at room temperature for 12 h, the reaction was diluted with ethyl acetate. The organic phase was washed sequentially with brine, 1N hydrochloric acid and 1N aqueous sodium hydroxide solution, dried over sodium sulfate, and evaporated in vacuo to yield the crude coupled product, which was used directly in the next step.

Step G: 3-[(2S,3S)-2-Amino-3-(4-fluorophenyl)-1-oxobutanyl]thiazolidine, trifluoroacetic acid salt

To a stirred solution of the product from Step E in dichloromethane (5 mL) was added trifluoroacetic acid (1 mL) at room temperature. After stirring at room temperature for 1 h, the solvent was removed in vacuo and the residue was purified by HPLC (YMC Pro-C18 column, gradient elution, 10-90% acetonitrile/water with 0.1% TFA) to give the title compound. LC/MS 269.1 (M+1).

EXAMPLE 2



•CF<sub>3</sub>CO<sub>2</sub>H

(2S)-1-[(2S,3S)-2-Amino-3-(4-fluorophenyl)-1-oxobutanyl]-2-cyanopyrrolidine, trifluoroacetic acid salt

- Step A: (βS)-N-(tert-Butoxycarbonyl)-4-fluoro-β-methyl-L-phenylalanyl-L-prolinamide
- To a stirred solution of (2S,3S)-2-azido-3-(4-fluorophenyl)butanoic acid (Example 1, Step D, 91.8 mg, 0.309 mmol) in anhydrous *N,N*-dimethylformamide (DMF, 1.5 mL) was added [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] (HATU, 141 mg, 0.371 mmol), 1-hydroxy-7-azabenzotriazole (HOAT, 50.5mg, 0.371 mmol), L-prolinamide (38.8 mg, 0.340 mmol) and *N,N'*-diisopropylethylamine (0.135 mL, 0.773 mmol). After stirring at room temperature for 16 h, the reaction was diluted with ethyl acetate. The organic phase was washed sequentially with water, saturated aqueous sodium bicarbonate solution and brine, dried (magnesium sulfate), and concentrated under reduced pressure. The residue was purified by preparative thin layer chromatography (silica, ethyl acetate eluant) to afford the title compound.

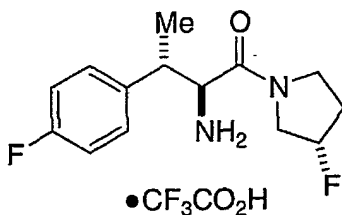
Step B: 1-[(βS)-N-(tert-Butoxycarbonyl)-4-fluoro-β-methyl-L-phenylalanyl]-2-cyanopyrrolidine

To a stirred solution of the product from Step A (91.7 mg, 0.233 mmol) in anhydrous DMF (1 mL) was added cyanuric chloride (86 mg, 0.466 mmol). After stirring at room temperature for 16 h, the reaction was diluted with ethyl acetate. The organic phase was washed sequentially with water, saturated aqueous sodium bicarbonate solution and brine, dried (magnesium sulfate), and concentrated under reduced pressure. Purification by preparative thin layer chromatography (silica, ethyl acetate eluant) afforded the title compound.

**Step C:** (2S)-1-[(2S,3S)-2-Amino-3-(4-fluorophenyl)-1-oxobutanyl]-2-cyanopyrrolidine, trifluoroacetic acid salt

To a stirred solution of 75.0 mg of the product from Step B in dichloromethane (1 mL) was added trifluoroacetic acid (1 mL) at room temperature. After stirring for 1 h, the solvent was removed in vacuo to give the title compound. LC/MS 275.1 (M+1).

### EXAMPLE 3



(3S)-1-[(2S,3S)-2-Amino-3-(4-fluorophenyl)-1-oxobutanyl]-3-fluoropyrrolidine, trifluoroacetic acid salt

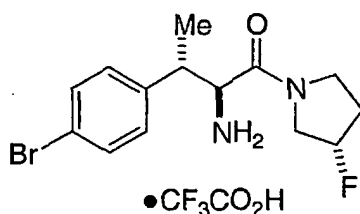
**Step A:** (3S)-1-[(2S,3S)-2-[(tert-Butoxycarbonyl)amino]-3-(4-fluorophenyl)-1-oxobutanyl]-3-fluoropyrrolidine

To a stirred solution of (βS)-N-(tert-butoxycarbonyl)-4-fluoro-β-methyl-L-phenylalanine (Example 1, Step E, 0.15 g, 0.51 mmol) in anhydrous DMF (2 mL) was added EDC (0.25 g, 1.33 mmol), HOBt (0.18 g, 1.33 mmol), (3S)-3-fluoropyrrolidine hydrochloride (0.18 g, 1.45 mmol) and N,N'-diisopropylethylamine (0.23 mL, 1.31 mmol). After stirring at room temperature for 12 h, the reaction was diluted with ethyl acetate. The organic phase was washed sequentially with brine, 1N hydrochloric acid and 1N aqueous sodium hydroxide solution, dried over sodium sulfate, and evaporated in vacuo to yield the crude coupled product, which was used directly for the next step.

**Step B:** (3S)-1-[(2S,3S)-2-Amino-3-(4-fluorophenyl)-1-oxobutanyl]-3-fluoropyrrolidine, trifluoroacetic acid salt

To a stirred solution of the product from Step A in dichloromethane (5 mL) was added trifluoroacetic acid (1 mL) at room temperature. After stirring at room temperature for 1 h, the solvent was removed in vacuo and the residue was purified by HPLC (YMC Pro-C18 column, gradient elution, 10-90% acetonitrile/water with 0.1% TFA) to give the title compound. LC/MS 269.0 (M+1).

**EXAMPLE 4**



(3S)-1-[(2S,3S)-2-Amino-3-(4-bromophenyl)-1-oxobutanyl]-3-fluoropyrrolidine, trifluoroacetic acid salt

**Step A:** (4R)-3-[(2E)-3-(4-Bromophenyl)prop-2-enoyl]-4-phenyl-1,3-oxazolidin-2-one

To a stirred solution of 4-bromocinnamic acid (5.79 g, 22.5 mmol) in anhydrous THF (250 mL) was added triethylamine (4.60 mL, 34.6 mmol) followed by trimethylacetyl chloride (3.54 mL, 24.7 mmol) at -78 °C. The resultant suspension was stirred at -78 °C for 15 min, 0 °C for 1 h, at then -78 °C for 15 min before being transferred via cannula into a slurry of lithium 4(R)-4-phenyl-2-oxazolidinone at 0 °C, which was prepared 15 min in advance at -78 °C by addition of *n*-butyllithium (19.1 mL, 30.5 mmol) to a solution of 4(R)-4-phenyl-2-oxazolidinone (5.0 g, 30.6 mmol) in anhydrous THF (150 mL) at -78 °C. The resultant slurry was stirred at -78 °C for 1 h and room temperature for 12 h. The reaction was quenched with saturated aqueous ammonium chloride solution. The organic phase was separated, concentrated in vacuo, and the crude product was used directly for the next step. LC/MS 372.0 (M+1).

**Step B:** (4R)-3-[(3R)-3-(4-Bromophenyl)butanoyl]-4-phenyl-1,3-oxazolidin-2-one

To a stirred solution of copper(II) bromide dimethylsulfide complex (8.78 g, 42.7 mmol) in THF (60 mL) and dimethylsulfide (30 mL) was added methylmagnesium bromide (12.7 mL, 3.0M in diethyl ether, 38.1 mmol) at -40 °C. The resultant mixture was stirred at -40



°C for 30 min, then warmed to -20 °C. The product from Step A (3.53 g, 9.48 mmol) in THF (30 mL) was added to the above reaction mixture over 1 h at -20 °C. The resultant mixture was stirred at -20 °C for 2 h, then slowly warmed to room temperature and stirred at room temperature for 12 h. The reaction was quenched by slow addition of saturated aqueous ammonium chloride solution. The organic phase was separated and the aqueous phase was extracted with two portions of ethyl acetate. The combined organic layers were washed with brine and concentrated in vacuo. Purification by flash chromatography (silica gel, 83:17 hexanes/ethyl acetate) afforded the desired product.

10 Step C:      (4R)-3-[(2R,3S)-2-Bromo-3-(4-bromophenyl)butanoyl]-4-phenyl-1,3-oxazolidin-2-one

To a stirred solution of the product from Step B (2.87 g, 7.39 mmol) in dichloromethane (40 mL) was added diisopropylethylamine (1.93 mL, 11.1 mmol) and dibutylborontriflate (9.6 mL, 1M solution in dichloromethane, 9.60 mmol) at -78 °C. The light yellow solution was stirred at -78 °C for 15 min, 0 °C for 1 h and re-cooled to -78 °C for 15 min. The above solution was transferred to a pre-cooled suspension of *N*-bromosuccinimide (3.93 g, 22.2 mmol) in dichloromethane (40 mL) via cannula. The resultant mixture was stirred at -78 °C for 1 h and 0 °C for 3 h. The reaction was quenched by addition of 0.5N aqueous sodium bisulfite solution. The organic phase was separated and the aqueous phase was extracted with two portions of ethyl acetate. The combined organic layers were washed with brine and concentrated in vacuo. Purification by flash chromatography (silica gel, 83:17 hexanes/ethyl acetate) afforded the desired product.

25 Step D:      (4R)-3-[(2S,3S)-2-Azido-3-(4-bromophenyl)butanoyl]-4-phenyl-1,3-oxazolidin-2-one

To a stirred solution of the product from Step C (2.71 g, 6.39 mmol) in acetonitrile (40 mL) was added tetramethylguanidinium azide (3.51 g, 22.2 mmol). The reaction was stirred at room temperature for 12 h. The solid was filtered off, and the filtrate was evaporated. The crude product was purified by flash chromatography (83:17 hexanes/ethyl acetate) to give the desired product.

Step E:      (2S,3S)-2-Azido-3-(4-bromophenyl)butanoic acid

To a stirred solution of the product from Step D (2.77 g, 6.23 mmol) in THF (60 mL) was added water (20 mL). The solution was stirred at 0 °C for 15 min, and then 30%

hydrogen peroxide (6.0 mL, 52.9 mmol) was added followed by slow addition of lithium hydroxide (0.50 g, 21.2 mmol). The resultant mixture was stirred at 0 °C for 4 h. The reaction was quenched by addition of saturated aqueous sodium sulfite solution and stirred at room temperature for 30 min. The aqueous phase was separated and washed with three portions of dichloromethane. The aqueous phase was then acidified to pH 1 with 3N hydrochloric acid and extracted with three portions of ethyl acetate. The ethyl acetate extracts were combined, dried over sodium sulfate, and evaporated in vacuo to give the product, which was used in the next step directly.

10 Step F: (3S)-1-[(2S,3S)-2-[(*tert*-Butoxycarbonyl)amino]-3-(4-bromophenyl)-1-oxobutanyl]-3-fluoropyrrolidine

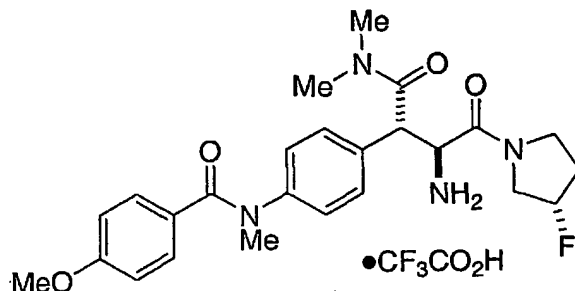
To 1.20 g (4.22 mmol) of acid dissolved in anhydrous DMF (10 mL) was added EDC (2.29 g, 11.9 mmol), HOBT (1.62 g, 11.9 mmol), (3S)-3-fluoropyrrolidine hydrochloride (1.50 g, 11.9 mmol) and *N,N'*-diisopropylethylamine (4.2 mL, 23.6 mmol). After stirring at room temperature for 12 h, the reaction was diluted with ethyl acetate. The organic phase was washed with brine, 1N hydrochloric acid and 1N aqueous sodium hydroxide solution, dried over sodium sulfate, and evaporated in vacuo to yield a yellow colored foam. To this foam was added 40 mL of dioxane, 4 mL of water and triphenylphosphine (4.70 g, 17.9 mmol). The reaction was heated at 90 °C for 12 h before it was cooled to room temperature. The solvent was removed in vacuo, and the residue was dissolved in 20 mL of dioxane and 20 mL of saturated aqueous sodium bicarbonate solution. To the resultant mixture was added 7.8 g of di-*tert*-butyldicarbonate (35.8 mmol). The reaction was stirred at room temperature for 12 h. The reaction mixture was diluted with ethyl acetate and acidified to pH 1 with 1N hydrochloric acid. The layers were separated, and the aqueous layer was extracted with two portions of ethyl acetate. The organic extracts were combined, washed with brine, dried over sodium sulfate, and concentrated in vacuo. Purification by flash chromatography (silica gel, 66:34 hexanes/ethyl acetate) afforded the desired product. LC/MS 429.1 (M+1).

30 Step G: (3S)-1-[(2S,3S)-2-Amino-3-(4-bromophenyl)-1-oxobutanyl]-3-fluoropyrrolidine, trifluoroacetic acid salt

To a stirred solution of the product from Step F (100 mg, 0.23 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (1 mL) at room temperature. After stirring at room temperature for 1 h, the solvent was removed in vacuo and the residue was

purified by HPLC (YMC Pro-C18 column, gradient elution, 10-90% acetonitrile/water with 0.1% TFA) to give the title compound. LC/MS 329.0 (M+1).

### EXAMPLE 5



N-(4-((1S,2S)-2-Amino-1-[(dimethylamino)carbonyl]-3-[(3S)-3-fluoropyrrolidin-1-yl]-3-oxopropyl)phenyl)-N-methyl-4-methoxybenzamide, trifluoroacetic acid salt

#### Step A: trans-4-(4-Bromophenyl)-3-buten-2-one

To 25.0 g (110 mmol) of 4-bromocinnamic acid dissolved in anhydrous dichloromethane (500 mL) was added EDC (28.8 g, 150 mmol), HOBT (20.3 g, 150 mmol), *N,O*-dimethylhydroxylamine hydrochloride (14.6 g, 150 mmol) and *N,N'*-diisopropylethylamine (23 mL, 150 mmol). After stirring at room temperature for 24 h, the reaction was concentrated then diluted with 400 mL of 10% aqueous hydrochloric acid. The resultant mixture was then extracted with three 300-mL portions of diethyl ether, the organic phases combined and washed sequentially with 10% hydrochloric acid, saturated aqueous sodium bicarbonate solution, and saturated aqueous brine (100 mL each). The organic phase was then dried over magnesium sulfate, filtered, and evaporated *in vacuo* to yield the Weinreb amide as a viscous oil that was used without further purification. To this oil was added 300 mL of anhydrous tetrahydrofuran and the resultant solution was cooled to  $-78^{\circ}\text{C}$ . To this solution was added 60 mL of methylmagnesium bromide (180 mmol, 3*N* in diethyl ether). The stirred mixture was allowed to warm slowly to  $0^{\circ}\text{C}$  over 1 h. The mixture was then quenched carefully with water and 5% aqueous hydrochloric acid (100 mL each) then concentrated to remove the tetrahydrofuran. The resultant mixture was extracted with three 300-mL portions of diethyl ether, the organic phases combined and washed sequentially with 5% hydrochloric acid, saturated aqueous sodium bicarbonate solution, and saturated aqueous brine (100 mL each). The organic phase was then dried over magnesium sulfate, filtered, and evaporated *in vacuo* to yield a viscous oil. The crude

material was then purified by flash chromatography on a Biotage® system (silica gel, 0 to 15% ethyl acetate/hexanes gradient) to give the title compound as pale yellow crystalline solid. LC/MS 225.0 (M+1), 227.0 (M+3).

5    Step B:            (2*S*,3*E*)-4-(4-Bromophenyl)-3-buten-2-ol

To 5.55 g (24.7 mmol) of the ketone from Step A dissolved in 100 mL of toluene was added 3.7 mL (3.7 mmol, 1*M* in toluene) of (*R*)-2-methyl-CBS-oxazaborolidine catalyst and the resultant mixture was stirred at ambient temperature for 15 min. The mixture was cooled to -78 °C and 4.0 mL (37.1 mmol) of catecholborane in 30 mL of toluene was added dropwise over  
10    30 min. After the addition, the slurry was stirred at -78 °C for 60 min while slowly turning homogeneous. The solution was then stirred at -78 °C an additional 4 h (reaction time varies from 4-24 h) until TLC revealed complete disappearance of starting material. Next, the reaction mixture was diluted with 100 mL of water and the resultant mixture was extracted with three 100-mL portions of diethyl ether. The organic phases were then combined and washed with two  
15    100-mL portions of 1 *N* NaOH aqueous solution, two 100 mL portions of 5% hydrochloric acid solution, 100-mL portions of saturated aqueous brine, dried over magnesium sulfate, filtered, and evaporated *in vacuo* to yield the crude waxy solid. The crude material was then purified by flash chromatography on a Biotage® system (silica gel, 0 to 20% ethyl acetate/hexanes gradient) to give the alcohol as a colorless crystalline solid. This compound was recrystallized in hexanes to  
20    yield the alcohol as colorless crystals (96% ee by Mosher ester analysis). LC/MS 209.0 (M-H<sub>2</sub>O+1), 211.0 (M-H<sub>2</sub>O+3).

Step C:            (1*S*,2*E*)-3-(4-Bromophenyl)-1-methylprop-2-enyl *N*-(*tert*-butoxycarbonyl)glycinate

25    To 12.6 g (55 mmol) of the alcohol from Step B dissolved in anhydrous dichloromethane (300 mL) was added EDC (23 g, 120 mmol), HOBT (16 g, 120 mmol), *N*-(*tert*-butoxycarbonyl)glycine (21 g, 120 mmol) and *N,N'*-diisopropylethylamine (19 mL, 120 mmol). After 5 h, the mixture was concentrated and diluted with 200 mL of 10% aqueous hydrochloric acid. The resultant mixture was then extracted with three 300-mL portions of diethyl ether, the  
30    organic phases combined and washed sequentially with 5% hydrochloric acid, saturated aqueous sodium bicarbonate solution, and saturated aqueous brine (100 mL each). The organic phase was then dried over magnesium sulfate, filtered, and evaporated *in vacuo* to yield the crude material as a viscous oil. The crude material was purified by flash chromatography on a Biotage® system

(silica gel, 0 to 20% ethyl acetate/hexanes gradient) to give the title compound as a colorless crystalline solid. LC/MS 328.1 (M-*t*Bu+1), 330.1 (M- *t*Bu+3).

**Step D:**      Methyl (βS)-4-Bromo-N-(tert-butoxycarbonyl)-β-[(1E)-prop-1-enyl]-L-phenylalaninate

5                      The ester from Step C (18.1 g, 47 mmol) in anhydrous tetrahydrofuran (50 mL) was added via cannula to 105 mL (105 mmol, 1M in tetrahydrofuran) of lithium hexamethyldisilazide solution precooled to -78 °C. After stirring for 10 min at that temperature, 55 mL of zinc chloride solution (55 mmol, 1M in diethyl ether) was added at -78 °C. The  
10                      resultant mixture was stirred at -78 °C for 5 h then allowed to warm slowly to room temperature over 3 h. After stirring an additional 2 h at room temperature, the mixture was quenched with water and 5% hydrochloric acid (100 mL each). The resultant mixture was then extracted with three 300-mL portions of ethyl acetate, the organic phases combined and washed sequentially  
15                      with 5% hydrochloric acid, saturated aqueous sodium bicarbonate solution, and saturated aqueous brine (200 mL each). The organic phase was then dried over magnesium sulfate, filtered, and evaporated *in vacuo* to yield the crude material as a yellow foam. LC/MS 384.1 (M+1), 386.1 (M+3). This crude material was dissolved in 500 mL of 1:1 diethyl ether/methanol and cooled to 0 °C. Trimethylsilyldiazomethane solution (75 mL, 150 mmol, 2M in hexanes)  
20                      was added in portions until a yellow color persisted. After warming to room temperature, the solution was stirred an additional 8 h, then concentrated *in vacuo*. The crude material was purified by flash chromatography on a Biotage® system (silica gel, 0 to 15% ethyl acetate/hexanes gradient) to give the title compound as a colorless oil. LC/MS 298.0 (M-Boc+1), 300.0 (M-Boc+3).

25   **Step E:**      (βS)-4-Bromo-N-(tert-butoxycarbonyl)-β-[(1E)-prop-1-enyl]-L-phenylalanine

                    To a solution of 25 g (62.8 mmol) of methyl (βS)-4-bromo-N-(tert-butoxycarbonyl)-β-[(1E)-prop-1-enyl]-L-phenylalaninate (Step D) in 600 mL of tetrahydrofuran (THF) was added in succession 200 mL of methanol and 200 mL (200 mmol) of 1N aqueous sodium hydroxide solution. The reaction mixture was stirred at ambient temperature for 3 h, and  
30                      then the methanol and THF were removed under reduced pressure. To the aqueous mixture was added 250 mL of 1N hydrochloric acid and the mixture was extracted with ethyl acetate (3 x 300 mL). The combined organic extracts were washed with brine (300 mL) then dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford the carboxylic acid, which was used without further purification.

Step F: (3S)-1-[(2S,3S,4E)-3-(4-Bromophenyl)-2-(tert-butoxycarbonylamino)hex-4-enoyl]-3-fluoropyrrolidine

To a solution of 2.00 g (5.21 mmol) of (βS)-4-bromo-*N*-(*tert*-butoxycarbonyl)-β-  
5 [(1*E*)-prop-1-enyl]-L-phenylalanine from Step E and 0.781 g (6.25 mmol) of (3*S*)-3-fluoropyrrolidine hydrochloride (Intermediate 1) in 50 mL of DMF were added 2.71 mL (15.6 mmol) of *N,N'*-diisopropylethylamine, 0.774 g (5.73 mmol) of HOBT, and 1.10 g (5.73 mmol) of EDC. After 16 h at ambient temperature, the reaction was quenched by the addition of 200 mL of 0.5 M aqueous sodium bicarbonate solution. The mixture was extracted with two 300-mL  
10 portions of ethyl acetate. The organic layers were washed with two additional 200-mL portions of 0.5 M aqueous sodium bicarbonate solution, brine, dried (magnesium sulfate) and concentrated *in vacuo* to give a clear oil. Purification by silica gel chromatography (20 - 50% ethyl acetate/hexanes gradient) afforded the title compound as a colorless oil. LC/MS 355.3 (M+1) and 357.3 (M+3).

15

Step G: (3S)-1-[(2S,3S)-3-(4-Bromophenyl)-2-(tert-butoxycarbonylamino)-3-(dimethylaminocarbonyl)-1-oxopropanyl]-3-difluoropyrrolidine

To solution of 2.37 g (11.1 mmol) of sodium periodate, 0.306 g (2.21 mmol) of potassium carbonate, and 0.087 g (0.550 mmol) of potassium permanganate in 30 mL of water  
20 was added 70 mL of *tert*-butanol at ambient temperature. The resulting suspension was added to a solution of 2.21 g (1.01 mmol) of (3*S*)-1-[(2*S*,3*S*,4*E*)-3-(4-bromophenyl)-2-(*tert*-butoxycarbonylamino)hex-4-enoyl]-3-fluoropyrrolidine from Step F in 20 mL of *tert*-butanol. The resulting mixture was then heated to 40 °C for 9 h. The mixture was then cooled to ambient temperature and poured onto 200 mL of 1 M aqueous sodium bisulfate solution. The resulting  
25 mixture was extracted with two 250-mL portions of ethyl acetate. The organic layers were washed with brine, dried (magnesium sulfate), and concentrated *in vacuo* to afford a yellow solid. This material was dissolved in 26 mL of DMF. To this solution was added 1.33 mL (2.65 mmol) of a 2.0 M solution of dimethylamine in THF, followed by 1.15 mL (6.63 mmol) of *N,N'*-diisopropylethylamine, 0.328 g (2.43 mmol) of HOBT, and 0.466 g (2.43 mmol) of EDC. After  
30 stirring for 16 h at ambient temperature, the reaction was diluted with 100 mL of 0.5 M aqueous sodium bicarbonate solution. The mixture was extracted with two 250-mL portions of ethyl acetate. The organic layers were washed with an additional two 100-mL portions of 0.5 M aqueous sodium bicarbonate solution and brine, then dried (magnesium sulfate) and concentrated *in vacuo* affording a yellow oil. Purification by silica gel chromatography (0 - 10% MeOH/ethyl

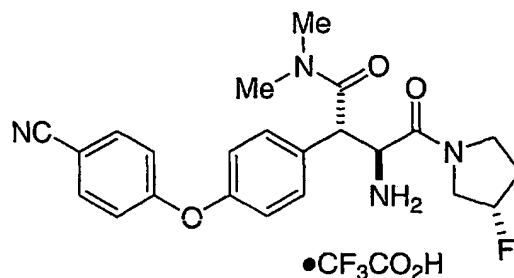
acetate gradient) afforded the title compound as a yellow solid. LC/MS 385.8 (M+1) and 387.8 (M+3).

5      Step H:      *N*-(4-[(1*S*,2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-1-[(dimethylamino)carbonyl]-3-[(3*S*)-3-fluoropyrrolidin-1-yl]-3-oxopropyl]phenyl)-*N*-methyl-4-methoxybenzamide

10      To a solution of 56.9 mg (0.117 mmol) of (3*S*)-1-[(2*S*,3*S*)-3-(4-bromophenyl)-2-(*tert*-butoxycarbonylamino)-3-(dimethylaminocarbonyl)-1-oxopropyl]-3-difluoropyrrolidine from Step G in 1 mL of toluene in a sealable tube were added 48.5 mg (0.293 mmol) of *N*-methyl-4-methoxybenzamide, 48.5 mg (0.351 mmol) of solid potassium carbonate, and 22.3 mg (0.117 mmol) of solid copper(I) iodide. To this mixture was added a solution of 0.0378 mL of *N,N'*-dimethylethylenediamine in 1 mL of toluene. The mixture was degassed with a stream of nitrogen for 10 min, then sealed and heated to 110 °C for 48 h. The mixture was cooled to ambient temperature, and the solids were triturated and filtered with a solution of 1:1:1 ethyl acetate/dichloromethane/methanol. The solution was concentrated *in vacuo*, and the resulting residue was purified by preparative thin layer chromatography (10% methanol/ethyl acetate),  
15      affording the title compound as a white solid. LC/MS 509.2 (M+1).

20      Step I:      *N*-(4-[(1*S*,2*S*)-2-Amino-1-[(dimethylamino)carbonyl]-3-[(3*S*)-3-fluoropyrrolidin-1-yl]-3-oxopropyl]phenyl)-*N*-methyl-4-methoxybenzamide, trifluoroacetic acid salt

25      To a solution of 17.6 mg (0.0346 mmol) of *N*-(4-[(1*S*,2*S*)-2-[(*tert*-butoxycarbonyl)amino]-1-[(dimethylamino)carbonyl]-3-[(3*S*)-3-fluoropyrrolidin-1-yl]-3-oxopropyl]phenyl)-*N*-methyl-4-methoxybenzamide from Step H in 1 mL of dichloromethane was added 1 mL of trifluoroacetic acid. After 1 h at ambient temperature, the solution was concentrated *in vacuo*. Purification by reverse-phase preparative HPLC (10% to 80% acetonitrile in water) afforded the title compound as a foaming white solid. LC/MS 471.2 (M+1).

EXAMPLE 6

5 (2S,3S)-3-Amino-2-[4-(4-cyanophenoxy)phenyl]-4-[(3S)-3-fluoropyrrolidin-1-yl]-N,N-dimethyl-4-oxobutanamide, trifluoroacetic acid salt

Step A: (3S)-1-[(2S,3S)-2-(tert-Butoxycarbonylamino)-3-(dimethylaminocarbonyl)-1-oxo-3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]propanyl]-3-fluoropyrrolidine

10 A mixture of 5.48 g (11.27 mmol) of the compound from Example 5, Step G, bis(pinacolato)diboron (5.72 g, 22.54 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (1.84 g, 2.25 mmol) and potassium acetate (3.32 g, 33.81 mmol) was purged with nitrogen. Methylsulfoxide (60 mL) was then added, the solution was degassed and refilled with nitrogen, and the reaction mixture was then warmed at 90 °C overnight. The resulting black mixture was cooled to room temperature, filtered through a pad of Celite, and the filter cake was washed with ethyl acetate. The combined filtrates were diluted with additional ethyl acetate (500 mL), washed sequentially with saturated aqueous sodium bicarbonate solution, water, and saturated brine, dried (magnesium sulfate) and concentrated under reduced pressure. The dark viscous residue was purified by flash chromatography (silica gel, methanol/ethyl acetate eluant) to afford the title compound. LC-MS 534.3 (M+1).

Step B: (3S)-1-[(2S,3S)-2-(tert-Butoxycarbonylamino)-3-(dimethylaminocarbonyl)-1-oxo-3-(4-hydroxyphenyl)propanyl]-3-fluoropyrrolidine

25 To a solution of 4.0 g (7.50 mmol) of material from Step A above in 75 mL of tetrahydrofuran at 0 °C was added 1.25 mL of an aqueous solution of 30% hydrogen peroxide. After 1 h, the solution was allowed to warm up to ambient temperature and stirring continued for 2 h. The reaction mixture was acidified with 1N hydrochloric acid to pH 4. Additional water



was added, and the aqueous layer was extracted with ethyl acetate (three times). The combined organic extracts were washed with saturated brine, dried (magnesium sulfate) and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (silica gel, methanol/ethyl acetate) to afford the title compound. LC-MS 424.2 (M+1).

5

Step C: (2S,3S)-3-[(*tert*-Butoxycarbonyl)amino]-2-[4-(4-cyanophenoxy)phenyl]-4-[(3S)-3-fluoropyrrolidin-1-yl]-*N,N*-dimethyl-4-oxobutanamide

To a suspension of 324 mg (0.766 mmol) of the compound from Step B above in 8 mL of dichloromethane was added 4-cyanophenylboronic acid (225 mg, 1.532 mmol), copper acetate (139 mg, 0.766 mmol), pyridine (0.31 mL, 3.830 mmol) and 4Å molecular sieves. The mixture was stirred under a balloon of air at ambient temperature for 40 h, and was then filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to afford an oil, which was purified by flash chromatography (silica gel, methanol/dichloromethane eluant) to afford the title compound. LC-MS 525.3 (M+1).

15

Step D: (2S,3S)-3-Amino-2-[4-(4-cyanophenoxy)phenyl]-4-[(3S)-3-fluoropyrrolidin-1-yl]-*N,N*-dimethyl-4-oxobutanamide, trifluoroacetic acid salt

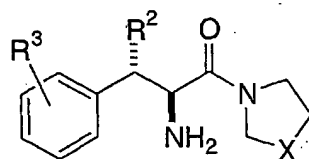
A solution of the compound (4.0 mg) from Step C above in dichloromethane (1 mL) was treated with trifluoroacetic acid (1 mL). After one h, the solution was concentrated under reduced pressure to afford the title compound. LC-MS 425.3 (M+1).

20

Essentially following the procedures outlined for Examples 1-6, Examples 7-26 listed in Table 1 were prepared.

25

TABLE 1



<u>Example</u>	<u>R<sup>3</sup></u>	<u>R<sup>2</sup></u>	<u>X</u>	<u>MS</u> (M+1)
7	4-OMe	Me	CF <sub>2</sub>	299.2

8	4-OMe	Me	(S)-CHF	281.0
9	3-F,5-F	Me	(S)-CHF	287.0
10	4-Cl	Me	(S)-CHF	285.0
11	4-F	Me	CF <sub>2</sub>	269.1
12	4-F	Et	(S)-CHF	283.1
13	4-Cl	Me	CF <sub>2</sub>	303.0
14	4-F	Et	CH <sub>2</sub>	265.1
15	4-CF <sub>3</sub>	Me	(S)-CHF	319.0
16	2-F,4-Cl	Me	(S)-CHF	303.0
17	4-[3-CF <sub>3</sub> -PhCON(Me)]	CONMe <sub>2</sub>	(S)-CHF	509.2
18	4-[4-Me-PhCON(Me)]	CONMe <sub>2</sub>	(S)-CHF	455.2
19	4-[4-Cl-PhCON(Me)]	CONMe <sub>2</sub>	(S)-CHF	475.2
20	4-[4-F-PhCON(Me)]	CONMe <sub>2</sub>	(S)-CHF	459.3
21	4-[3,4-diCl-PhCON(Me)]	CONMe <sub>2</sub>	(S)-CHF	509.2
22	4-[3,5-diCl-PhCON(Me)]	CONMe <sub>2</sub>	(S)-CHF	509.2
23	4-[4-OCF <sub>3</sub> -PhCON(Me)]	CONMe <sub>2</sub>	(S)-CHF	525.2
24	4-[PhCH <sub>2</sub> CH <sub>2</sub> CON(Me)]	CONMe <sub>2</sub>	(S)-CHF	469.3
25	4-[PhCON(Me)]	CONMe <sub>2</sub>	(S)-CHF	441.2
26	4-(3,4-diCl-PhO)	CONMe <sub>2</sub>	(S)-CHF	468.0

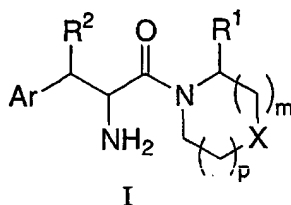
EXAMPLE OF A PHARMACEUTICAL FORMULATION

As a specific embodiment of an oral pharmaceutical composition, a 100 mg potency tablet is composed of 100 mg of any of the compounds of the present invention, 268 mg microcrystalline cellulose, 20 mg of croscarmellose sodium, and 4 mg of magnesium stearate. The active, microcrystalline cellulose, and croscarmellose are blended first. The mixture is then lubricated by magnesium stearate and pressed into tablets.

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above. The specific pharmacological responses observed may vary according to and depending upon the particular active compounds selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

## WHAT IS CLAIMED IS:

1. A compound of structural formula I:



- 5 or a pharmaceutically acceptable salt thereof; wherein  
each n is independently 0, 1, or 2;  
m and p are independently 0 or 1;  
q is 1 or 2;

- 10 X is CH<sub>2</sub>, S, CHF, or CF<sub>2</sub>;

Ar is phenyl, unsubstituted or substituted with one to five R<sup>3</sup> substituents;

R<sup>1</sup> is hydrogen or cyano;

15

R<sup>2</sup> is selected from the group consisting of

- 20 C<sub>1-10</sub> alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents  
independently selected from halogen or hydroxy,  
C<sub>2-10</sub> alkenyl, wherein alkenyl is unsubstituted or substituted with one to five  
substituents independently selected from halogen or hydroxy,  
(CH<sub>2</sub>)<sub>n</sub>-aryl, wherein aryl is unsubstituted or substituted with one to five substituents  
independently selected hydroxy, halogen, CO<sub>2</sub>H, C<sub>1-6</sub> alkyloxycarbonyl, C<sub>1-6</sub>  
alkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted  
with one to five halogens,  
25 (CH<sub>2</sub>)<sub>n</sub>-heteroaryl, wherein heteroaryl is unsubstituted or substituted with one to three  
substituents independently selected from hydroxy, halogen, CO<sub>2</sub>H, C<sub>1-6</sub>  
alkyloxycarbonyl, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are  
unsubstituted or substituted with one to five halogens,

- (CH<sub>2</sub>)<sub>n</sub>-heterocyclyl, wherein heterocyclyl is unsubstituted or substituted with one to three substituents independently selected from oxo, hydroxy, halogen, CO<sub>2</sub>H, C<sub>1-6</sub> alkyloxycarbonyl, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,
- 5 (CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub> cycloalkyl, wherein cycloalkyl is unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, CO<sub>2</sub>H, C<sub>1-6</sub> alkyloxycarbonyl, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,
- (CH<sub>2</sub>)<sub>n</sub>COOH,
- 10 (CH<sub>2</sub>)<sub>n</sub>COOC<sub>1-6</sub> alkyl,
- (CH<sub>2</sub>)<sub>n</sub>CONR<sup>4</sup>R<sup>5</sup>, wherein R<sup>4</sup> and R<sup>5</sup> are independently selected from the group consisting of hydrogen, tetrazolyl, thiazolyl, (CH<sub>2</sub>)<sub>n</sub>-phenyl, (CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub> cycloalkyl, and C<sub>1-6</sub> alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens and wherein phenyl and cycloalkyl are unsubstituted or
- 15 substituted with one to five substituents independently selected from halogen, hydroxy, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens;
- or R<sup>4</sup> and R<sup>5</sup> together with the nitrogen atom to which they are attached form a heterocyclic ring selected from azetidine, pyrrolidine, piperidine, piperazine, and
- 20 morpholine wherein said heterocyclic ring is unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens; and
- wherein any methylene (CH<sub>2</sub>) carbon atom in R<sup>2</sup> is unsubstituted or substituted with one
- 25 to two groups independently selected from halogen, hydroxy, C<sub>1-4</sub> alkyl, and C<sub>1-4</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens;
- each R<sup>3</sup> is independently selected from the group consisting of
- 30 halogen,  
cyano,  
hydroxy,  
C<sub>1-6</sub> alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens,  
C<sub>1-6</sub> alkoxy, wherein alkoxy is unsubstituted or substituted with one to five halogens,

phenyloxy, unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, CO<sub>2</sub>H, cyano, C<sub>1-6</sub> alkyloxycarbonyl, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens;

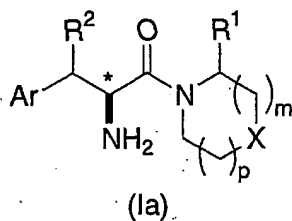
- 5 (CH<sub>2</sub>)<sub>n</sub>-NR<sup>4</sup>R<sup>5</sup>,  
 (CH<sub>2</sub>)<sub>n</sub>-CONR<sup>4</sup>R<sup>5</sup>,  
 (CH<sub>2</sub>)<sub>n</sub>-OCONR<sup>4</sup>R<sup>5</sup>,  
 (CH<sub>2</sub>)<sub>n</sub>-SO<sub>2</sub>NR<sup>4</sup>R<sup>5</sup>,  
 (CH<sub>2</sub>)<sub>n</sub>-SO<sub>2</sub>R<sup>6</sup>,  
 10 (CH<sub>2</sub>)<sub>n</sub>-NR<sup>7</sup>SO<sub>2</sub>R<sup>6</sup>,  
 (CH<sub>2</sub>)<sub>n</sub>-NR<sup>7</sup>CONR<sup>4</sup>R<sup>5</sup>,  
 (CH<sub>2</sub>)<sub>n</sub>-NR<sup>7</sup>COR<sup>7</sup>,  
 (CH<sub>2</sub>)<sub>n</sub>-NR<sup>7</sup>CO<sub>2</sub>R<sup>6</sup>,  
 (CH<sub>2</sub>)<sub>n</sub>-COOH,  
 15 (CH<sub>2</sub>)<sub>n</sub>-COOC<sub>1-6</sub> alkyl,  
 (CH<sub>2</sub>)<sub>q</sub>-aryl, wherein aryl is unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, CO<sub>2</sub>H, C<sub>1-6</sub> alkyloxycarbonyl, C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,  
 20 (CH<sub>2</sub>)<sub>q</sub>-heteroaryl, wherein heteroaryl is unsubstituted or substituted with one to three substituents independently selected from hydroxy, halogen, CO<sub>2</sub>H, C<sub>1-6</sub> alkyloxycarbonyl, C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens;  
 (CH<sub>2</sub>)<sub>q</sub>-heterocyclyl, wherein heterocyclyl is unsubstituted or substituted with one to  
 25 three substituents independently selected from oxo, hydroxy, halogen, CO<sub>2</sub>H, C<sub>1-6</sub> alkyloxycarbonyl, C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,  
 (CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub> cycloalkyl, wherein cycloalkyl is unsubstituted or substituted with one to  
 three substituents independently selected from halogen, hydroxy, C<sub>1-6</sub> alkyl, and  
 30 C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,  
 wherein any methylene (CH<sub>2</sub>) carbon atom in R<sup>3</sup> is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, C<sub>1-4</sub> alkyl, and C<sub>1-4</sub>

alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens;

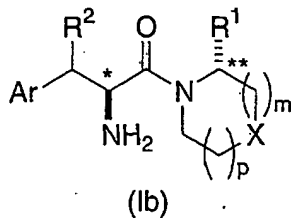
$R^6$  is independently selected from the group consisting of tetrazolyl, thiazolyl,  $(CH_2)_n$ -phenyl,  $(CH_2)_n$ -C<sub>3-6</sub> cycloalkyl, and C<sub>1-6</sub> alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens and wherein phenyl and cycloalkyl are unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens, and wherein any methylene ( $CH_2$ ) carbon atom in  $R^6$  is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C<sub>1-4</sub> alkyl unsubstituted or substituted with one to five halogens; and

each  $R^7$  is hydrogen or  $R^6$ .

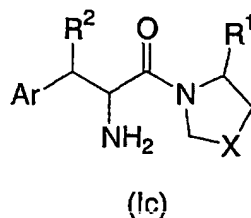
2. The compound of Claim 1 wherein the carbon atom marked with an \* has the stereochemical configuration as depicted in formula Ia:



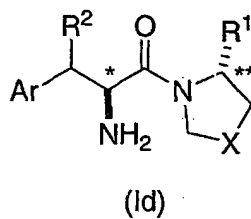
3. The compound of Claim 2 wherein the carbon atom attached to  $R^1$  marked with an \*\* has the stereochemical configuration as depicted in formula Ib:



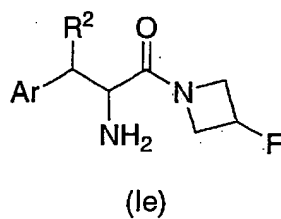
4. The compound of Claim 1 of the structural formula Ic:



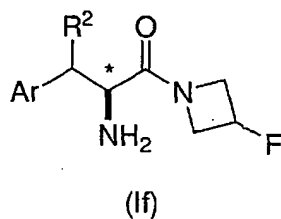
5. The compound of Claim 4 wherein the carbon atom marked with an \* and the carbon atom marked with an \*\* have the stereochemical configurations as depicted in formula Id:



6. The compound of Claim 1 of the structural formula Ie

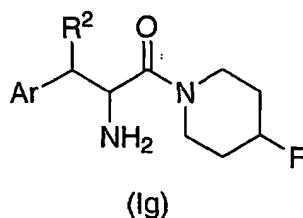


7. The compound of Claim 6 wherein the carbon atom marked with an \* has the stereochemical configuration as depicted in formula If:

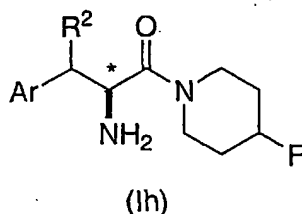




8. The compound of Claim 1 of the structural formula Ig



9. The compound of Claim 8 wherein the carbon atom marked with an \* has the stereochemical configuration as depicted in formula Ih:



5

10. The compound of Claim 1 wherein R<sup>2</sup> is selected from the group consisting of

- C<sub>1-6</sub> alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents independently selected from halogen or hydroxy,
- 10 C<sub>2-6</sub> alkenyl, wherein alkenyl is unsubstituted or substituted with one to five substituents independently selected from halogen or hydroxy,
- (CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub> cycloalkyl, wherein cycloalkyl is unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, CO<sub>2</sub>H, C<sub>1-6</sub> alkyloxycarbonyl, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are
- 15 unsubstituted or substituted with one to five halogens,
- (CH<sub>2</sub>)<sub>n</sub>COOH,
- (CH<sub>2</sub>)<sub>n</sub>COOC<sub>1-6</sub> alkyl, and
- (CH<sub>2</sub>)<sub>n</sub>CONR<sup>4</sup>R<sup>5</sup>, wherein R<sup>4</sup> and R<sup>5</sup> are independently selected from the group consisting of hydrogen, tetrazolyl, thiazolyl, (CH<sub>2</sub>)<sub>n</sub>-phenyl, (CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub>
- 20 cycloalkyl, and C<sub>1-6</sub> alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens and wherein phenyl and cycloalkyl are unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens;

or R<sup>4</sup> and R<sup>5</sup> together with the nitrogen atom to which they are attached form a heterocyclic ring selected from pyrrolidine, piperidine, piperazine, and morpholine wherein said heterocyclic ring is unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens; and

wherein any methylene (CH<sub>2</sub>) carbon atom in R<sup>2</sup> is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, C<sub>1-4</sub> alkyl, and C<sub>1-4</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens.

10

11. The compound of Claim 10 wherein R<sup>2</sup> is selected from the group consisting of

C<sub>1-3</sub> alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents independently selected from halogen or hydroxy,  
 15 CH<sub>2</sub>-C<sub>3-6</sub> cycloalkyl,  
 COOH,  
 COOC<sub>1-6</sub> alkyl, and  
 CONR<sup>4</sup>R<sup>5</sup>, wherein R<sup>4</sup> and R<sup>5</sup> are independently selected from the group consisting of hydrogen, tetrazolyl, thiazolyl, (CH<sub>2</sub>)<sub>n</sub>-phenyl, (CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub> cycloalkyl, and C<sub>1-6</sub>  
 20 alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens and wherein phenyl and cycloalkyl are unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens;

25

or R<sup>4</sup> and R<sup>5</sup> together with the nitrogen atom to which they are attached form a heterocyclic ring selected from pyrrolidine, piperidine, piperazine, and morpholine wherein said heterocyclic ring is unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens.

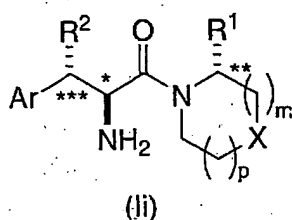
30

12. The compound of Claim 11 wherein R<sup>2</sup> is selected from the group consisting of

methyl,  
 ethyl,

CH<sub>2</sub>-cyclopropyl,  
 COOH,  
 COOMe,  
 COOEt,  
 5 CONMe<sub>2</sub>,  
 CONH<sub>2</sub>,  
 CONHMe,  
 CONHEt,  
 pyrrolidin-1-ylcarbonyl,  
 10 azetidin-1-ylcarbonyl, and  
 [(tetrazol-5-yl)amino]carbonyl.

13. The compound of Claim 1 wherein the carbon atom marked with an \*, the carbon atom attached to R<sup>1</sup> marked with an \*\*, and the carbon atom attached to R<sup>2</sup> marked with an \*\*\* have the stereochemical configurations as depicted in formula II:



R<sup>2</sup> is selected from the group consisting of

C<sub>1-6</sub> alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents

independently selected from halogen or hydroxy,

20 (CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub> cycloalkyl,

COOH,

COOC<sub>1-6</sub>alkyl, and

CONR<sup>4</sup>R<sup>5</sup>, wherein R<sup>4</sup> and R<sup>5</sup> are independently selected from the group consisting of

hydrogen, tetrazolyl, thiazolyl, (CH<sub>2</sub>)<sub>n</sub>-phenyl, (CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub> cycloalkyl, and C<sub>1-6</sub>

25 alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens and

wherein phenyl and cycloalkyl are unsubstituted or substituted with one to five

substituents independently selected from halogen, hydroxy, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub>

alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five

halogens;

5 or wherein R<sup>4</sup> and R<sup>5</sup> together with the nitrogen atom to which they are attached form a heterocyclic ring selected from pyrrolidine, piperidine, piperazine, and morpholine wherein said heterocyclic ring is unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens; and

each R<sup>3</sup> is independently selected from the group consisting of:

10 halogen,  
hydroxy,  
C<sub>1-6</sub> alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens,  
C<sub>1-6</sub> alkoxy, wherein alkoxy is unsubstituted or substituted with one to five halogens,  
phenyloxy, unsubstituted or substituted with one to three substituents independently  
15 selected from halogen, hydroxy, cyano, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy, wherein  
alkyl and alkoxy are unsubstituted or substituted with one to five halogens; and  
(CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub> cycloalkyl, wherein cycloalkyl is unsubstituted or substituted with one to  
three substituents independently selected from halogen, hydroxy, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub>  
alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five  
20 halogens.

20 14. The compound of Claim 13 wherein R<sup>2</sup> is selected from the group  
consisting of

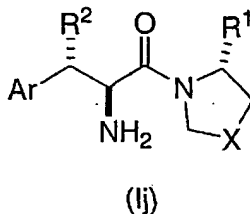
25 methyl,  
ethyl,  
CH<sub>2</sub>-cyclopropyl,  
COOH,  
COOMe,  
COOEt,  
CONMe<sub>2</sub>,  
30 CONH<sub>2</sub>,  
CONHMe,  
CONHEt,  
pyrrolidin-1-ylcarbonyl,  
azetidin-1-ylcarbonyl, and

[(tetrazol-5-yl)amino]carbonyl.

15. The compound of Claim 14 wherein R<sup>3</sup> is selected from the group consisting of:

- 5        fluoro,  
        chloro,  
        bromo,  
        trifluoromethyl,  
        trifluoromethoxy, and  
 10       methoxy.

16. The compound of Claim 1 of the structural formula Ij



wherein X is CH<sub>2</sub>, S, CHF, or CF<sub>2</sub>;

- 15    Ar is phenyl, unsubstituted or substituted with one to five R<sup>3</sup> substituents;  
       R<sup>1</sup> is hydrogen or cyano;

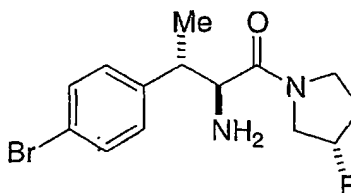
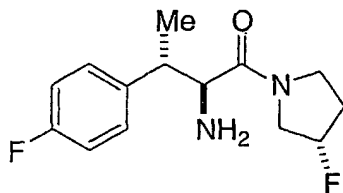
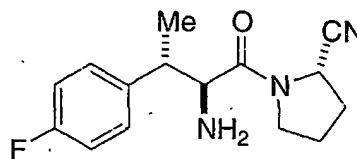
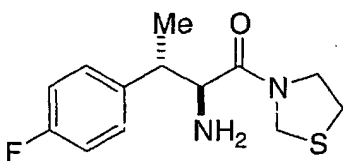
R<sup>2</sup> is selected from the group consisting of

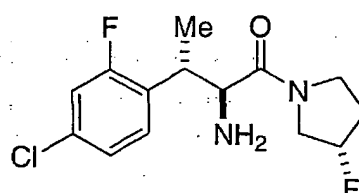
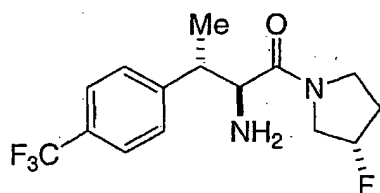
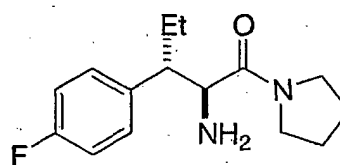
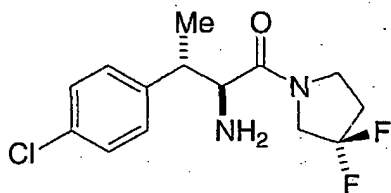
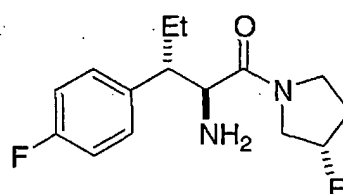
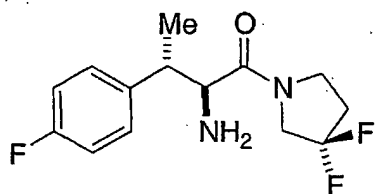
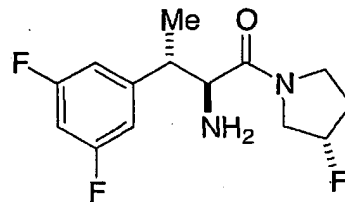
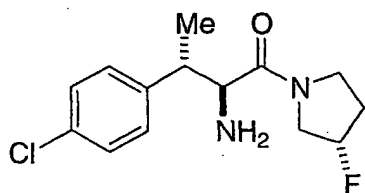
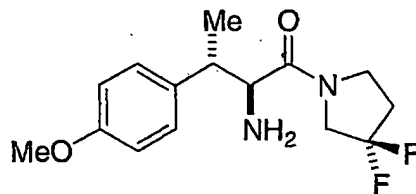
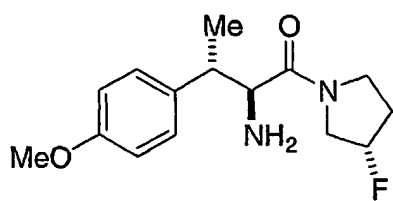
- C<sub>1-6</sub> alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents  
 20       independently selected from halogen or hydroxy,  
       (CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub> cycloalkyl,  
       COOH,  
       COOC<sub>1-6</sub> alkyl, and  
 25       CONR<sup>4</sup>R<sup>5</sup>, wherein R<sup>4</sup> and R<sup>5</sup> are independently selected from the group consisting of  
       hydrogen, tetrazolyl, thiazolyl, (CH<sub>2</sub>)<sub>n</sub>-phenyl, (CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub> cycloalkyl, and C<sub>1-6</sub>  
       alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens and  
       wherein phenyl and cycloalkyl are unsubstituted or substituted with one to five  
       substituents independently selected from halogen, hydroxy, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub>

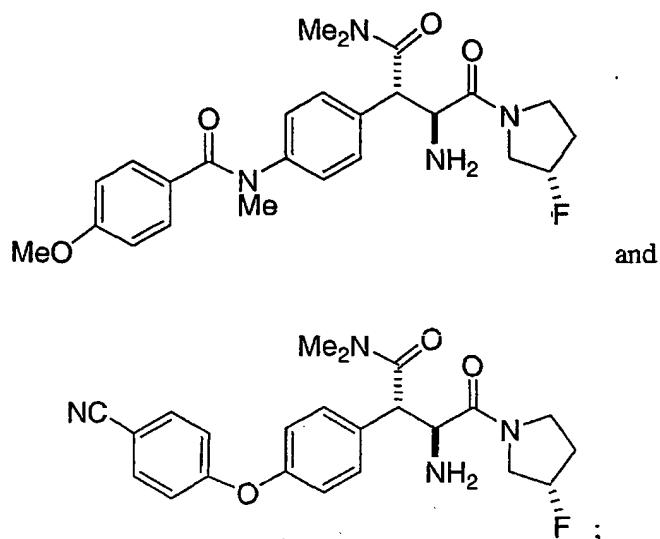
alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens;  
 or R<sup>4</sup> and R<sup>5</sup> together with the nitrogen atom to which they are attached form a heterocyclic ring selected from pyrrolidine, piperidine, piperazine, and morpholine wherein said heterocyclic ring is unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens; and

- each R<sup>3</sup> is independently selected from the group consisting of:  
 halogen,  
 C<sub>1-6</sub> alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens,  
 C<sub>1-6</sub> alkoxy, wherein alkoxy is unsubstituted or substituted with one to five halogens,  
 phenyloxy, unsubstituted or substituted with one to three substituents independently selected from halogen and cyano, and  
 phenyl(CH<sub>2</sub>)<sub>n</sub>CON(Me)-, wherein phenyl is unsubstituted or substituted with one to three substituents independently selected from halogen, trifluoromethyl, and C<sub>1-4</sub> alkyl.

17. The compound of Claim 16 of the structural formula selected from the group consisting of







or a pharmaceutically acceptable salt thereof.

- 5                    18.    A pharmaceutical composition which comprises a compound of Claim 1  
and a pharmaceutically acceptable carrier.
- 10                   19.    A method for inhibiting dipeptidyl peptidase-IV enzyme activity in a  
mammal in need thereof which comprises the administration to the mammal of an effective  
amount of a compound of Claim 1.
- 15                   20.    A method for treating diabetes in a mammal in need thereof which  
comprises the administration to the mammal of a therapeutically effective amount of a compound  
of Claim 1.
- 20                   21.    A method for treating non-insulin dependent (Type 2) diabetes in a  
mammal in need thereof which comprises the administration to the mammal of a therapeutically  
effective amount of a compound of Claim 1.
- 20                   22.    A method for treating hyperglycemia in a mammal in need thereof which  
comprises the administration to the mammal of a therapeutically effective amount of a compound  
of Claim 1.



23. A method for treating obesity in a mammal in need thereof which comprises the administration to the mammal of a therapeutically effective amount of a compound of Claim 1.

5                   24. A method for treating one or more lipid disorders selected from the group of dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL and high LDL in a mammal in need thereof which comprises the administration to the mammal of a therapeutically effective amount of a compound of Claim 1.

10                   25. A method for treating in a mammal in need thereof one or more conditions selected from the group consisting of (1) hyperglycemia, (2) low glucose tolerance, (3) insulin resistance, (4) obesity, (5) lipid disorders, (6) dyslipidemia, (7) hyperlipidemia, (8) hypertriglyceridemia, (9) hypercholesterolemia, (10) low HDL levels, (11) high LDL levels, (12) atherosclerosis and its sequelae, (13) vascular restenosis, (14) irritable bowel syndrome, (15) inflammatory bowel disease, including Crohn's disease and ulcerative colitis, (16) other inflammatory conditions, (17) pancreatitis, (18) abdominal obesity, (19) neurodegenerative disease, (20) retinopathy, (21) nephropathy, (22) neuropathy, (23) Syndrome X, (24) ovarian hyperandrogenism (polycystic ovarian syndrome), and other disorders where insulin resistance is a component, wherein the method comprises the administration to the mammal a therapeutically effective amount of a compound of Claim 1.

26. The pharmaceutical composition of Claim 18 further comprising one or more additional active ingredients selected from the group consisting of:

- 25                   (a) a second dipeptidyl peptidase IV inhibitor;
- (b) an insulin sensitizer selected from the group consisting of a PPAR $\gamma$  agonist, a PPAR $\alpha/\gamma$  dual agonist, a PPAR $\alpha$  agonist, a biguanide, and a protein tyrosine phosphatase-1B inhibitor;
- 30                   (c) an insulin or insulin mimetic;
- (d) a sulfonylurea or other insulin secretagogue;
- (e) an  $\alpha$ -glucosidase inhibitor;
- (f) a glucagon receptor antagonist;
- (g) GLP-1, a GLP-1 mimetic, or a GLP-1 receptor agonist;
- (h) GIP, a GIP mimetic, or a GIP receptor agonist;
- (i) PACAP, a PACAP mimetic, or a PACAP receptor agonist;

(j) a cholesterol lowering agent such as (i) HMG-CoA reductase inhibitor, (ii) sequestrant, (iii) nicotinyl alcohol, nicotinic acid or a salt thereof, (iv) PPAR $\alpha$  agonist, (v) PPAR $\alpha$ / $\gamma$  dual agonist, (vi) inhibitor of cholesterol absorption, (vii) acyl CoA:cholesterol acyltransferase inhibitor, and (viii) anti-oxidant;

- 5           (k) a PPAR $\delta$  agonist;  
          (l) an antiobesity compound;  
          (m) an ileal bile acid transporter inhibitor;  
          (n) an anti-inflammatory agent; and  
          (o) an antihypertensive agent.

10

27.   The pharmaceutical composition of Claim 26 wherein the PPAR $\alpha$ / $\gamma$  dual agonist is KRP-297.

- 15       28.   A method of treating diabetes in a mammal in need thereof comprising administering to the mammal a therapeutically effective amount of a compound of Claim 1 in combination with the PPAR $\alpha$ / $\gamma$  dual agonist KRP-297.

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(54) Title: PHENYLALANINE DERIVATIVES AS DIPEPTIDYL PEPTIDASE INHIBITORS FOR THE TREATMENT OR PREVENTION OF DIABETES

(57) Abstract: The present invention is directed to phenylalanine derivatives which are inhibitors of the dipeptidyl peptidase-IV enzyme ("DP-IV inhibitors") and which are useful in the treatment or prevention of diseases in which the dipeptidyl peptidase-IV enzyme is involved, such as diabetes and particularly type 2 diabetes. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which the dipeptidyl peptidase-IV enzyme is involved.

WO 2004/050022 A3

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/37825

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/397, 31/40, 31/426, 31/445; C07D 205/04, 207/04, 295/192  
US CL : 514/210.17, 330, 365, 423; 546/226; 548/200, 540, 953

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
U.S. : 514/210.17, 330, 365, 423; 546/226; 548/200, 540, 953

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
CAS ONLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	WO 03/002530 A (SMITHKLINE BEECHAM CORPORATION) 09 January 2003 (09.01.2003)	

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
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"P" document published prior to the international filing date but later than the priority date claimed	

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- (71) Applicant (for all designated States except US): **MERCK & CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **DUFFY, Joseph, L.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **MATHVINK, Robert, J.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **WEBER, Ann, E.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **XU, Jinyou** [CN/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- (74) Common Representative: **MERCK & CO., INC.**; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (regional): ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
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(54) Title: PHENYLALANINE DERIVATIVES AS DIPEPTIDYL PEPTIDASE INHIBITORS FOR THE TREATMENT OR PREVENTION OF DIABETES

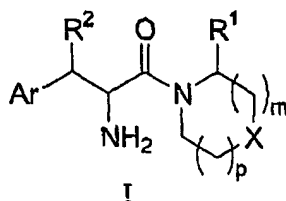
(57) Abstract: The present invention is directed to phenylalanine derivatives which are inhibitors of the dipeptidyl peptidase-IV enzyme ("DP-IV inhibitors") and which are useful in the treatment or prevention of diseases in which the dipeptidyl peptidase-IV enzyme is involved, such as diabetes and particularly type 2 diabetes. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which the dipeptidyl peptidase-IV enzyme is involved.

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## AMENDED CLAIMS

[Received by the International Bureau on 18 August 2004 (18.08.04)]

1. A compound of structural formula I:



5 or a pharmaceutically acceptable salt thereof; wherein  
 each n is independently 0, 1, or 2;  
 m and p are independently 0 or 1;  
 q is 1 or 2;

10 X is CH<sub>2</sub>, S, CHF, or CF<sub>2</sub>;

Ar is phenyl, unsubstituted or substituted with one to five R<sup>3</sup> substituents;

R<sup>1</sup> is hydrogen;

15

R<sup>2</sup> is selected from the group consisting of

C<sub>1-10</sub> alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents  
 independently selected from halogen or hydroxy,

C<sub>2-10</sub> alkenyl, wherein alkenyl is unsubstituted or substituted with one to five  
 substituents independently selected from halogen or hydroxy,

20

(CH<sub>2</sub>)<sub>n</sub>-aryl, wherein aryl is unsubstituted or substituted with one to five substituents  
 independently selected hydroxy, halogen, CO<sub>2</sub>H, C<sub>1-6</sub> alkyloxycarbonyl, C<sub>1-6</sub>  
 alkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted  
 with one to five halogens,

25

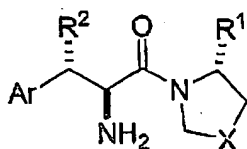
(CH<sub>2</sub>)<sub>n</sub>-heteroaryl, wherein heteroaryl is unsubstituted or substituted with one to three  
 substituents independently selected from hydroxy, halogen, CO<sub>2</sub>H, C<sub>1-6</sub>  
 alkyloxycarbonyl, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are  
 unsubstituted or substituted with one to five halogens,

[(tetrazol-5-yl)amino]carbonyl.

15. The compound of Claim 14 wherein R<sup>3</sup> is selected from the group consisting of:

- 5        fluoro,  
        chloro,  
        bromo,  
        trifluoromethyl,  
        trifluoromethoxy, and  
 10       methoxy.

16. The compound of Claim 1 of the structural formula Ij



(Ij)

wherein X is CH<sub>2</sub>, S, CHF, or CF<sub>2</sub>;

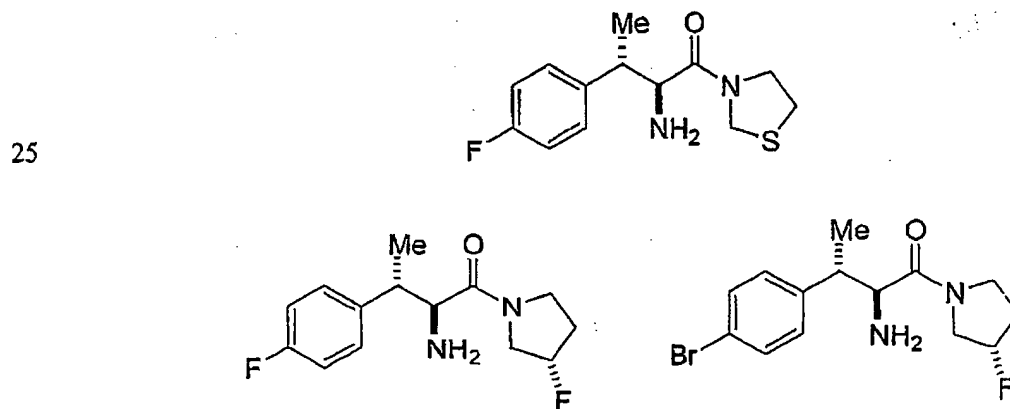
- 15    Ar is phenyl, unsubstituted or substituted with one to five R<sup>3</sup> substituents;  
      R<sup>1</sup> is hydrogen;

R<sup>2</sup> is selected from the group consisting of

- 20       C<sub>1-6</sub> alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents  
          independently selected from halogen or hydroxy,  
        (CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub> cycloalkyl,  
        COOH,  
        COOC<sub>1-6</sub> alkyl, and  
 25       CONR<sup>4</sup>R<sup>5</sup>, wherein R<sup>4</sup> and R<sup>5</sup> are independently selected from the group consisting of  
          hydrogen, tetrazolyl, thiazolyl, (CH<sub>2</sub>)<sub>n</sub>-phenyl, (CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub> cycloalkyl, and C<sub>1-6</sub>  
          alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens and  
          wherein phenyl and cycloalkyl are unsubstituted or substituted with one to five  
          substituents independently selected from halogen, hydroxy, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub>

- alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens;  
or R<sup>4</sup> and R<sup>5</sup> together with the nitrogen atom to which they are attached form a heterocyclic ring selected from pyrrolidine, piperidine, piperazine, and morpholine wherein said heterocyclic ring is unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens; and
- 10 each R<sup>3</sup> is independently selected from the group consisting of:  
halogen,  
C<sub>1-6</sub> alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens,  
C<sub>1-6</sub> alkoxy, wherein alkoxy is unsubstituted or substituted with one to five halogens,  
15 phenyloxy, unsubstituted or substituted with one to three substituents independently selected from halogen and cyano, and  
phenyl(CH<sub>2</sub>)<sub>n</sub>CON(Me)-, wherein phenyl is unsubstituted or substituted with one to three substituents independently  
20 selected from halogen, trifluoromethyl, and C<sub>1-4</sub> alkyl.

17. The compound of Claim 16 of the structural formula selected from the group consisting of





Statement under Article 19(1)

Claims 1, 16 and 17 of the international application have been amended to exclude compounds disclosed in WO 03/002530 cited in the International Search Report . The present amendment does not introduce new matter and is fully supported by Applicants' description. The present amendment has no impact on the description and the drawings of the international application.

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GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR,  
KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK,  
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30 September 2004

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tion II

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